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THE UNIVERSITY OF ALBERTA

TOWARDS THE SYNTHESIS OF LEUCOMYCIN A_3

by

© JAMES MICHAEL DIAKUR

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1980

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled

"TOWARDS THE SYNTHESIS OF LEUCOMYCIN A_3"

submitted by JAMES MICHAEL DIAKUR
in partial fulfilment of the requirements
for the degree of MASTER OF SCIENCE.

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Date Feb 29, 1980

To BERNADETTE, My Wife

ABSTRACT

In the field of antibiotics, the total syntheses of penicillins and cephalosporins, and tetracyclins have already been accomplished. The macrolide antibiotics were the only remaining major family of antibiotics that presented a challenge to synthetic organic chemists. Furthermore, the 16-membered macrolides were of clinical and therapeutic interest as a result of their significant biological activity.

This thesis describes the successful synthesis of the two units, C_1-C_9 and C_{11}-C_{15}, of leuconolide A_3, a 16-membered aglycone derived from the antibiotic produced by Streptomyces kitasatoensis. Our approach involved the synthesis of an analogue of the Djerassi-Prelog lactonic acid intermediate used in the synthesis of methymycin. Such an analogue was chosen since it has all the stereochemical characteristics present in the C_3-C_9 segment of the target leuconolide. A sequence of reactions beginning with the pyrolysis product of a mixture of norbornadiene dimers led to the key lactonic acid. Subsequent condensation with a novel magnesium reagent yielded the desired C_1-C_9 unit. This nine carbon unit contains three important features vital to our synthetic approach. First of all, this segment contains all of the stereochemical character-

istics found in the C_1-C_9 portion of the leucomycin aglycone. Secondly, carbon-9 can be activated for subsequent condensation with the optically active C_{11}-C_{15} unit; and, thirdly, carbon-1 contains the required functionality for the final lactonization step.

During the synthesis of these antibiotic segments, it was necessary to study the properties of a relatively unknown protecting group. The results are found in Part Two of this thesis. Also discussed in this section is the selective and direct activation of O-esters.

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To my Parents
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for "producing" a project!

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NOTE

It should be noted that in Chapter 4, the compounds are numbered from 1 to 89. The experimental for the compounds numbered 100 to 121 in this Chapter are reported elsewhere.[106] Therefore the compounds referred to in Chapter 4 correspond to the structures reported in this Chapter only.

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PART I: MACROLIDE ANTIBIOTICS

CHAPTER 1: INTRODUCTION

In 1950, Brockmann and Henkel[1] isolated a novel lactonic natural product from a Streptomyces organism. This new substance was named pikromycin. Since then, several other antimicrobially and chemically related antibiotics have been isolated from the same organisms. By the end of 1957, the gross structures of four members of this new family, including methymycin,[2] erythromycin A,[3] and B,[4] and carbomycin A (magnamycin)[5-7] had been elucidated. Classical chemical degradations demonstrated that each of these compounds contains a lactone incorporated in a medium or large-size ring system. Furthermore, the ring was found to be liberally substituted with methyl groups. Due to the structural similarities between these antibiotics, Woodward[5a] proposed the family name "macrolide". This rapidly growing family now includes well over one hundred lactonic natural products.

During these last two decades, comprehensive X-ray crystallographic, ^{1}H- and ^{13}C-NMR, and mass spectroscopic data obtained from a few representative macrolides, yielded much valuable information concerning the structural, stereochemical, and conformational properties of these compounds.[8-12]

These studies revealed unique structural features which attracted the interest of synthetic organic chemists. Thus we have witnessed in recent years, several major accomplishments in this area including several total syntheses.[13-18]

A brief outline of the chemistry and biochemistry of macrolide antibiotics is presented in this chapter.

A) STRUCTURE AND CLASSIFICATION

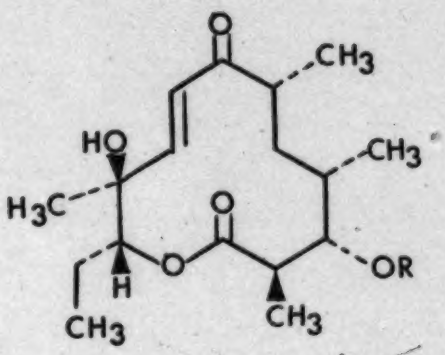
The structure of macrolide antibiotics has been the topic of several recent reviews[19-21] and these compounds have been classified according to their structures. It was found that many of these antibiotics could be classified as either "polyoxo", "polyene", or "ionophoric". There were several additional medium-size ring macrolides which have not thus far grown into large families.

I "POLYOXO" MACROLIDES

Of the more than one hundred macrolide antibiotics now known, at least half of them can be categorized in the "polyoxo" sub-group. These compounds are usually 12-, 14- or 16-membered lactones. Important characteristics of this sub-group are: (1) a systematic array of substituents, and (2) the linkage of one or more sugars. Typical examples include methymycin 1, pikromycin 2, erythromycin A 3 and B 3a, leucomycin A_3 4 and tylosin 5.[22] Structures of the sugars are shown in Figure 1.

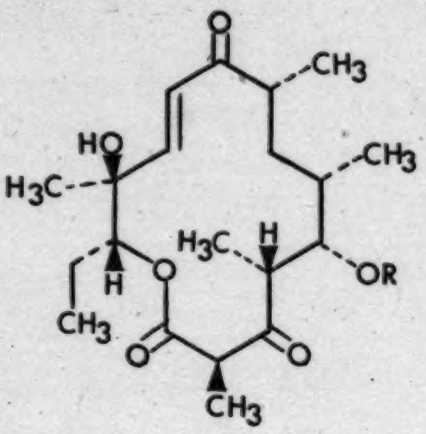
II "POLYENE" MACROLIDES

Structurally, compounds of the "polyene" sub-group contain only a few alkyl (mostly methyl) substituents and



1

R = Desosaminyl



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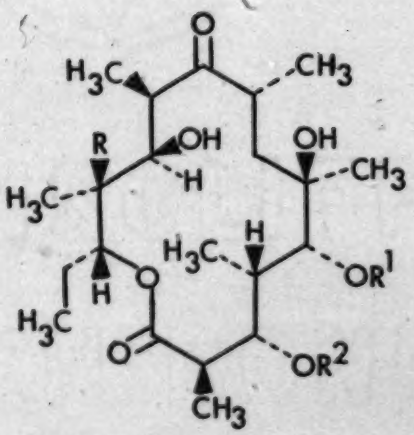
R = Desosaminyl

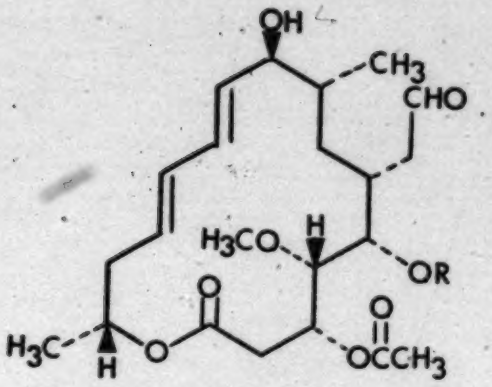


3 R = OH

3a R = H

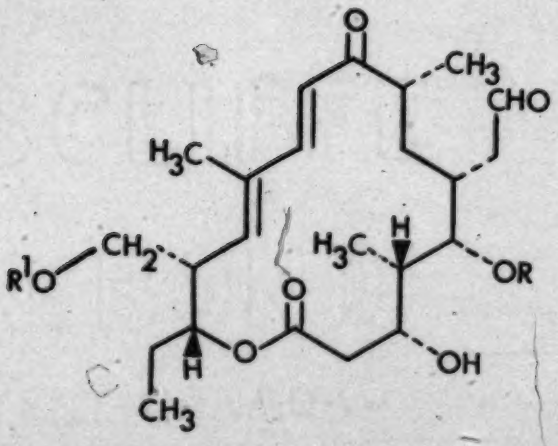
R^1 = Desosaminyl

R^2 = Cladinosyl



4

R = (Isovaleryl)-
mycarosyl-
mycaminosyl

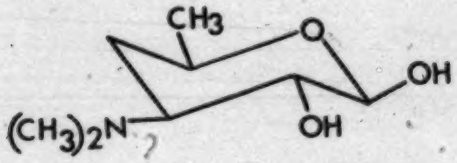


5

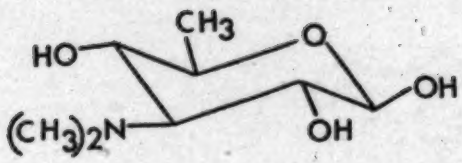
R = Mycarosyl - mycaminosyl

R^1 = Mycinosyl

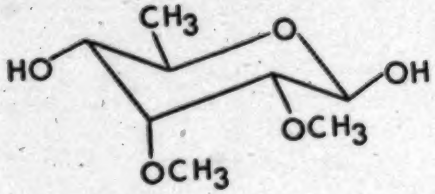
Figure 1: The Macrolide Sugars



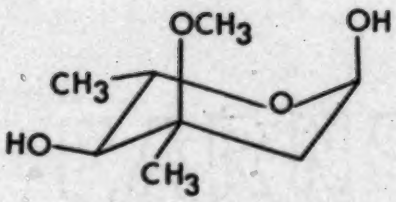
D-Desosamine



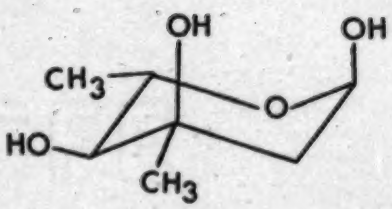
D-Mycaminose



D-Mycinose

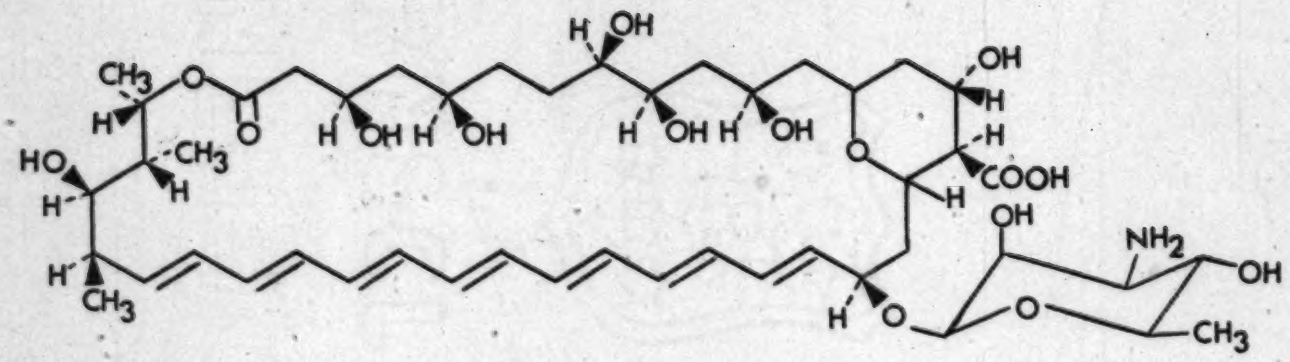


L-Cladinose



L-Mycarose

are characterized by a conjugated polyene consisting of up to as many as seven E double bonds. These molecules possess distinct hydrophilic (polyhydroxyl) and hydrophobic (polyene) regions as exemplified by amphotericin B 6.[23] Polyene macrolides generally exhibit strong antifungal activity.



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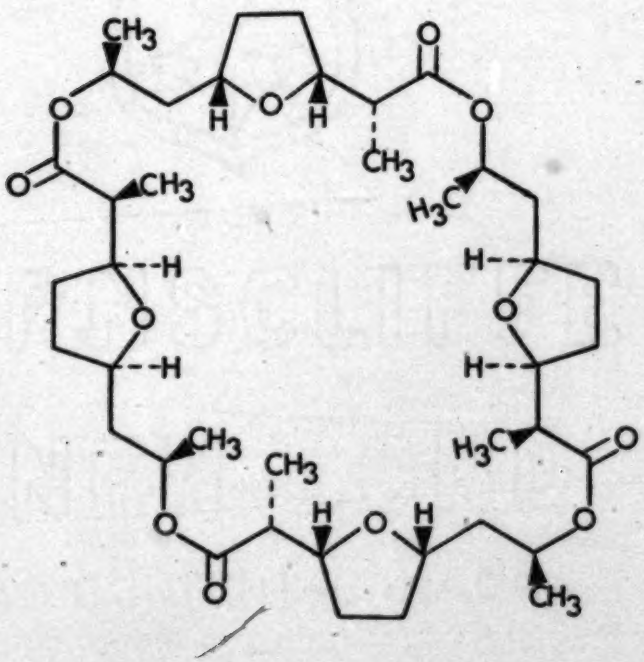
III "IONOPHORIC" MACROLIDES

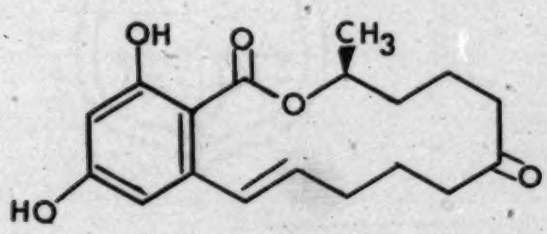
The major feature common to macrolides of the "ionophoric" sub-group is incorporation of two or more lactone groups (oligonolide) into a very large ring system. Most interesting is the hydrophilic "hole" these molecules possess, allowing them to bind and transport alkali metal cations in biological systems. The tetrolide nonactin 7[14,24] is a typical representative.



7

IV OTHER MACROLIDES

Included in this category are antibiotics which consist of a medium-size ring system and originate from either molds or bacteria. There are not sufficient members to date to form separate sub-groups. A few examples are zearalenone 8[25] (from Gibberella zeae), curvarin 9[26] (from a Curvalaria species), pyrenophorin 10[27] (from Pyrenophora avenae and Stemphylium radicinum), vermiculine 10a[28] (from Penicillium vermiculatum), and brefeldin A 11[29] (from Penicillium, Curvularia, and Ascochyla).



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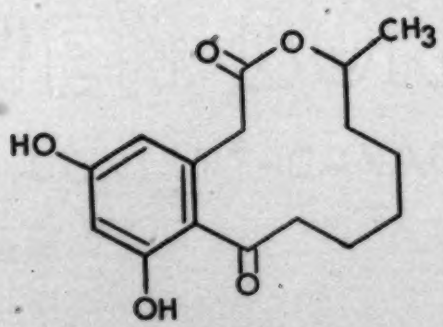

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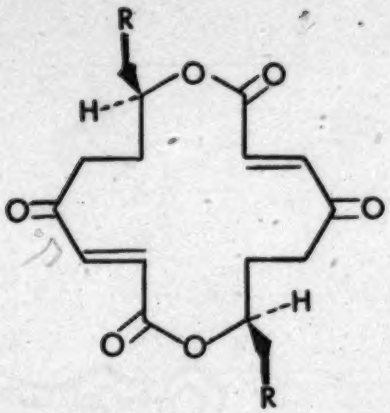
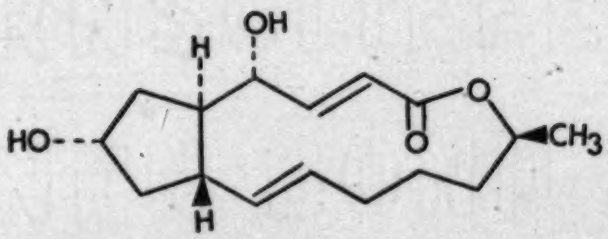


10 R = H

10a R = $COCH_3$



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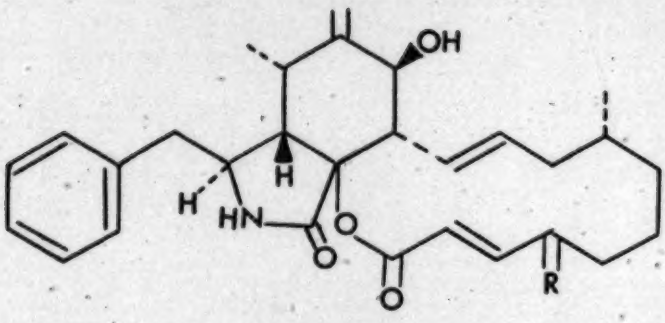


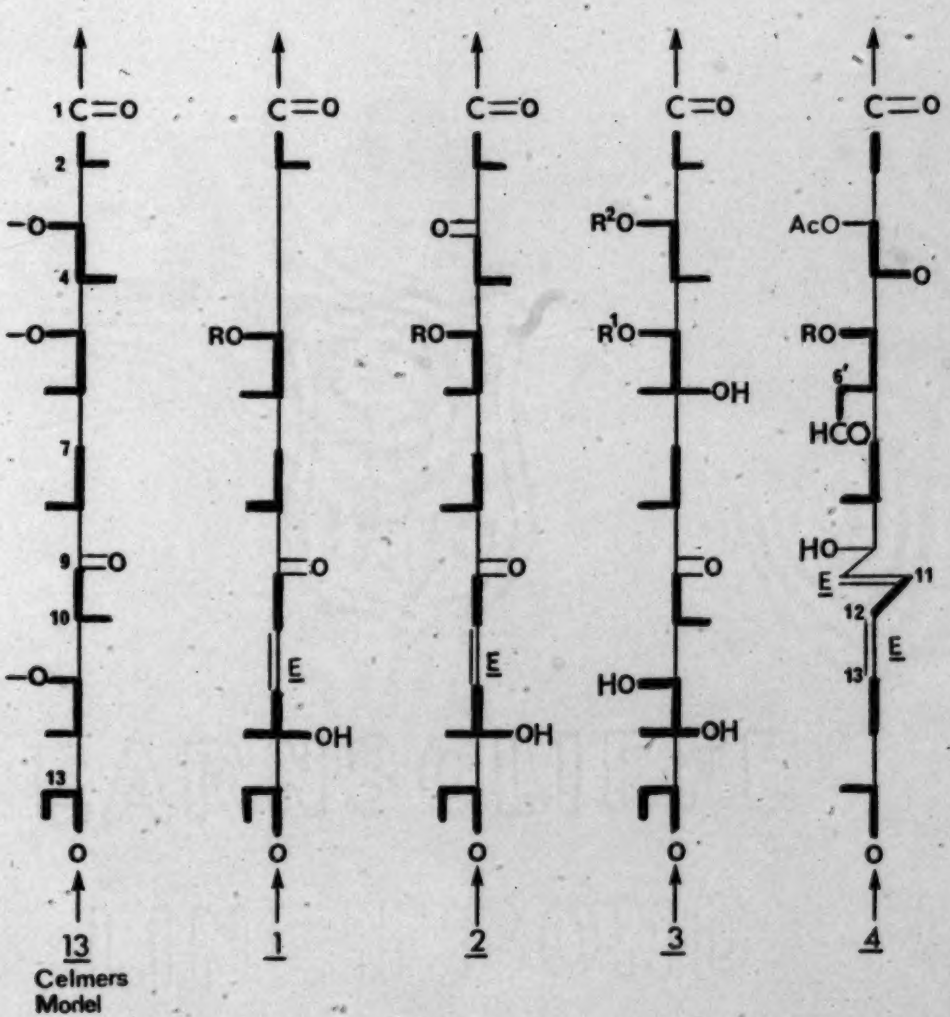
12a R = O
12b R = OH, H

The cytochalasans 12,[30] which possess very useful biological properties, are also classified under this subgroup. Some of their biological activities include antitumor, antibiotic, and cytostatic action. This family consists of 13- or 14-membered ring compounds originating from the corresponding cyclic ketone via Baeyer-Villiger type oxidation at a late stage of the biosynthesis.[31]

B) STEREOCHEMISTRY

The arrangement of the substituents attached to the lactone framework of "polyoxo" macrolides appears to be remarkably systematic and can be correlated to Celmer's model 13[11] shown in Figure 2. It can be seen that methymycin 1, pikromycin 2 and erythromycin A 3 correlate quite well. Information concerning the stereochemistry of leuco-

Figure 2: Celmer's Stereochemical Model



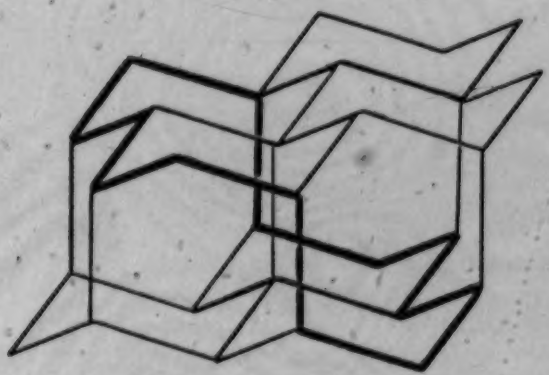
mycin 4[32] is available from X-ray data and confirms the indicated stereochemistry. An excellent fit can be achieved for this macrolide by inserting the extra two achiral carbon atoms (C_{10} and C_{11}) between C_9 and C_{10} of Celmer's model 13. This remarkable model has also been used to correct previously misassigned stereochemistry and to date, no contradictions have been found!

C) CONFORMATION

Owing to their chemotherapeutic importance, the 14-membered macrolides, such as erythromycins A and B, became readily available and were the first compounds of this class to undergo intense conformational analysis.

In 1965, Celmer suggested a model[33] for the preferred conformation of erythronolide B based on Dale's[34] proposed diamond lattice conformation of cyclotetradecane. This model, shown in Figure 3, was consistent with ^{1}H-NMR spectral data, mainly in terms of the dihedral angles obtained from the Karplus equation, however, it was found to be inconsistent with previous X-ray results. For example, the X-ray data of erythromycin B[35] indicated that the C_6-OH, C_9=O, and C_1=O (lactone) groups were syn to each other, and that all of the C-O axes of these groups were nearly parallel. The Celmer-Dale model had correctly assigned the syn orientation of the C_6-OH and C_9=O groups, however, it had placed

Figure 3: Conformation of Erythronolide B



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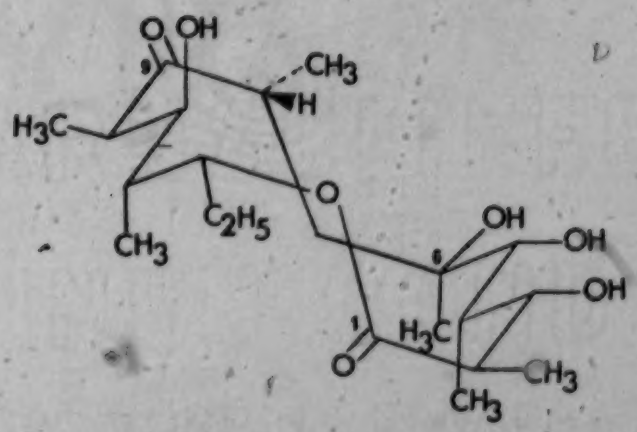
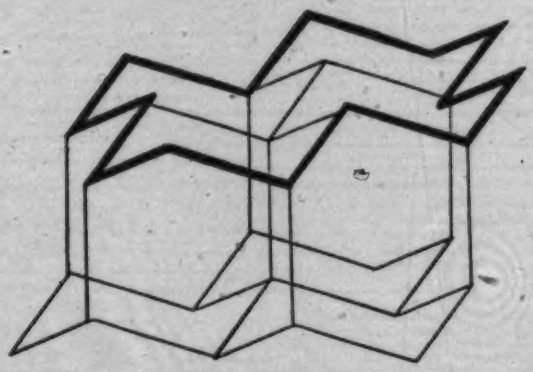


14

Figure 3 (Continued)



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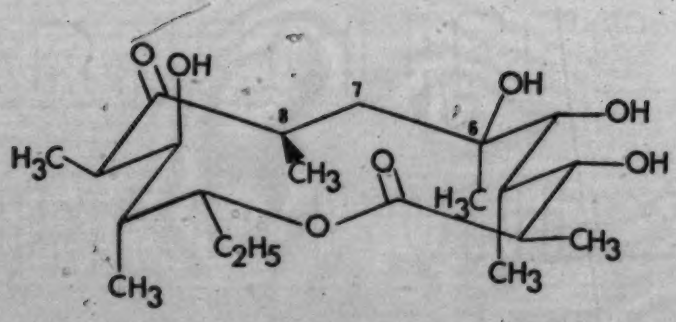


16

these groups anti to the lactone carbonyl. The resulting C-O axes were oriented in different directions. Furthermore, the crystal structure implied a rather flat molecule contrary to model 14. Another interesting observation was the fact that all of the vicinal proton-proton coupling constants[36] were either in the 10-12 Hz or 0-2 Hz range, and showed little or no solvent and temperature dependence. These results strongly implied a rigid ring system with restricted conformational freedom in solution leading to the conclusion that the preferred conformation in solution was not very much different in geometry from that of the crystal structure. Taking these facts into account, the Perun model 15 and 16[36] was proposed. This model restricted rotation along the C_7-C_8 axis thereby achieving syn orientation of both C_9=O and C_6-OH while minimizing the 1,3-interaction between the C_4 and C_6 methyl groups. An excellent fit with CD and ^{1}H- and ^{13}C-NMR data[37-39] was obtained in this way. This model also accounted for the possible hydrogen bonding between C_6-OH and C_9=O, and between C_{11}-OH and C_1=O as indicated by the ^{13}C-NMR parameters.

Inspection of CPK models of erythronolide B has revealed an additional structural feature, that is; the O-containing substituents (OH and sugar) appear on the same side of the molecule while the alkyl groups are located on the opposite side.

Even though the conformation of the 14-membered lactones has been reported, that of the 16-membered macrolide antibiotics still remains to be determined.

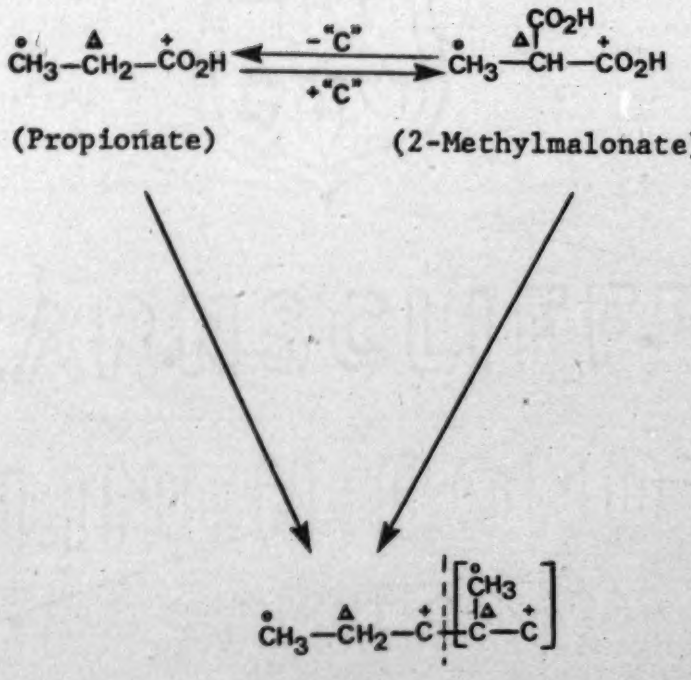
D) BIOGENESIS

The "polyoxo" macrolide antibiotics 1 to 5 display many common features in their biogenesis.[19] These macrolides originate from simple metabolic intermediates such as acetate, propionate, malonate, 2-methylmalonate, butyrate (or 2-ethylmalonate) in a manner analogous to saturated long-chain fatty acids. Typically, monomers activated at the carboxyl group, such as thiol esters of coenzyme A, condense in a rapid stepwise sequence with their carboxylated derivatives (malonate, 2-methylmalonate, and 2-ethylmalonate derivatives) to yield long-chain polyoxo fatty acids. These fatty acids can lactonize after a minimum of one biological reduction. The distinguishing feature between the biosynthesis of the macrolide lactones and the formation of saturated fatty acids is that in the former, the process of chain extension is independent of modification of the β-oxo function introduced at each stage.

Based on the overall similarity between the biosynthesis of fatty acids and that of macrolides, it was suggested that the erythronolides are produced from one

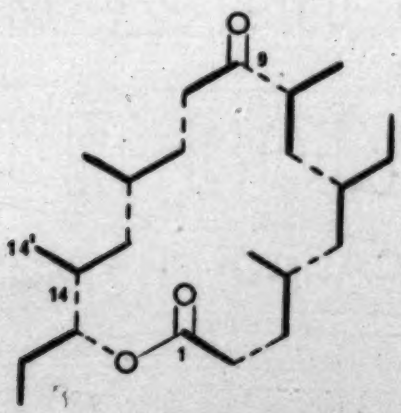
propionate and six 2-methylmalonate units by a General Fatty Acid Synthase (GFAS). This scheme has been confirmed by radioactive labelling experiments and from ^{13}C-NMR studies[40,41] and is shown in Figure 4. Lactonization, which precedes glycoside formation, yields the aglycone of erythronolide B.

Figure 4: GFAS of Erythronolide



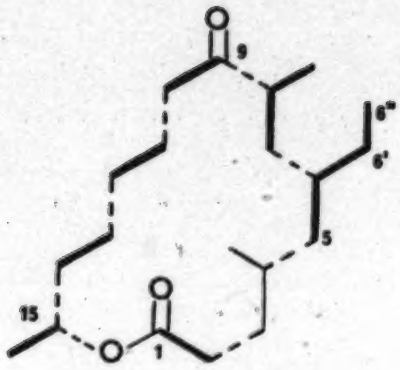
The macrolides methymycin and pikromycin have been found to be biogenetically similar to erythromycin. The major difference arises from the fact that they are not exclusively derived from propionate/2-methylmalonate, but have one unit originating from acetate/malonate.[42]

The biosynthetic scheme for 16-membered macrolide antibiotics has recently received much attention.[43-44] With respect to the lactone ring, these macrolide antibiotics can be classified into two groups: (1) the tylosin group, and (2) the leucomycin-magnamycin group. The tylosin group 17 is biogenetically similar to the erythromycin group and is largely derived from propionate with one biogenetic unit deriving from butyrate/2-ethylmalonate (GFAS: Pr, Mal, 2-MeMal, 2-EtMal).[43,44] The aldehyde group originates from the methyl position of the butyrate. Tylosin also consists of a disaccharide unit and a sugar residue attached to the hydroxylated C_{14}, methyl group.



17

Acetate Propionate Butyrate



18

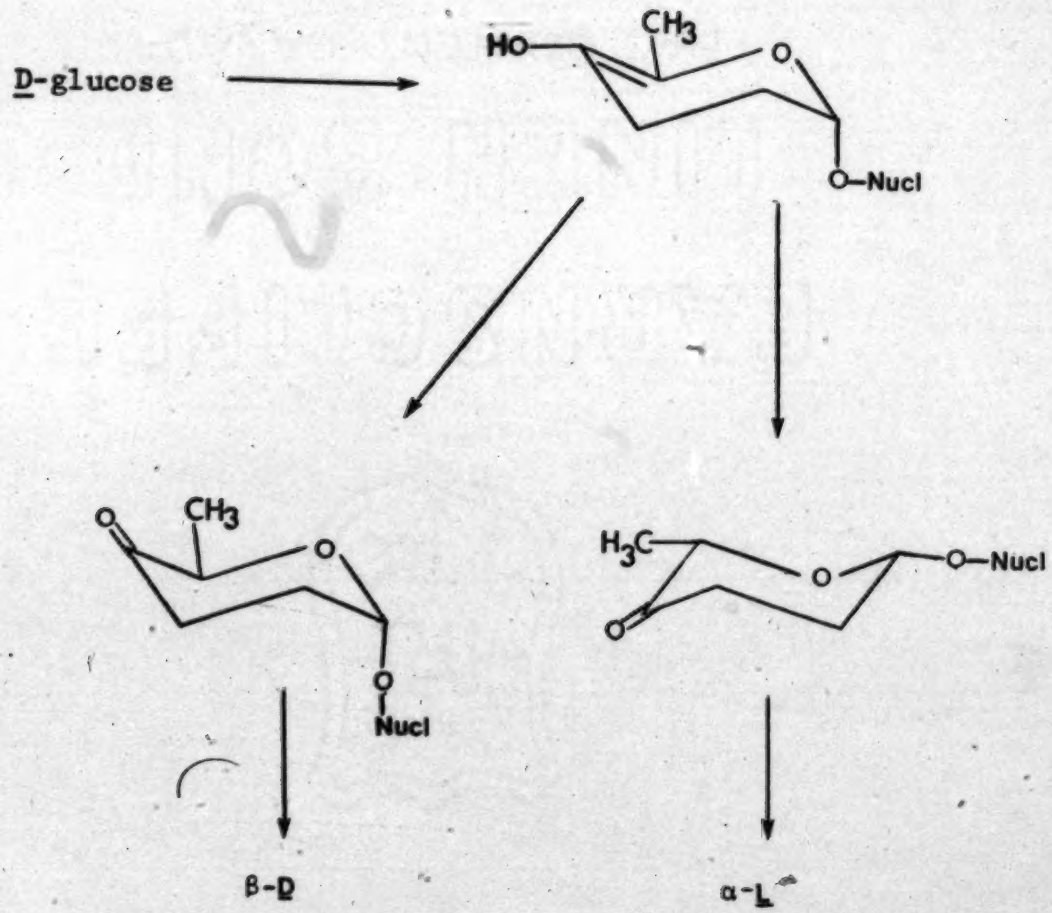
Acetate Propionate Butyrate

The second group of 16-membered macrolides, including carbomycin A (magnamycin) and the leucomycins, is derived from acetate/malonate units along with one propionate/2-methylmalonate unit and one butyrate/2-ethylmalonate unit 18. Butyrate was again found to be the source of the aldehyde moiety. The source of the C_3 and C_4 carbons of tylosin is known to be 2-methylmalonate, however, the origin of these carbons in the carbomycin skeleton remains to be found.[45] Evidence from studies on tylosin suggests possible biosynthesis from an acyl intermediate which could be formed after the 15-oxo or 15-hydroxy acid leaves the GFAS responsible for its formation.[46] A detailed discussion of the biosynthesis of leucomycin is postponed until Chapter 2.

The biogenesis of the macrolide sugars will now be outlined. D-glucose has been shown to be the primary building block of the macrolide sugars.[41] Thus incubation

of Streptomyces erythreus with D-glucose-1-^{14}C, -2-^{14}C, or -6-^{14}C, resulted in labelling concentrated at the corresponding carbon of desosamine. This, in essence, requires that the carbon chain of glucose must not be cleaved during the formation of these macrolide sugars. Although methionine is not involved in the biosynthesis of methonolide or erythronolide, labelling studies have shown that it is incorporated into the sugars desosamine and cladinose. The position of the label was determined by degradation of the sugars originating from the methyl-^{14}C methionine precursor. It was found that all the radioactivity in desosamine was located in the dimethylamino function, whereas in cladinose, the label was equally distributed between the O-methyl and the C-methyl at C_3. To account for these results, Celmer[42] proposed that D-glucose is bound to a nucleotide during its conversion to the macrolide 6-deoxy sugars as illustrated in Figure 5. This accounted for the fact that all macrolides have the same absolute configuration at their anomeric centers and implied that the necessary conversions could be carried out without opening of the glucose ring. The nucleotide is retained in the intermediates until final transfer of the deoxy sugar to the macrolide lactone.

Figure 5: Biosynthesis of Sugars



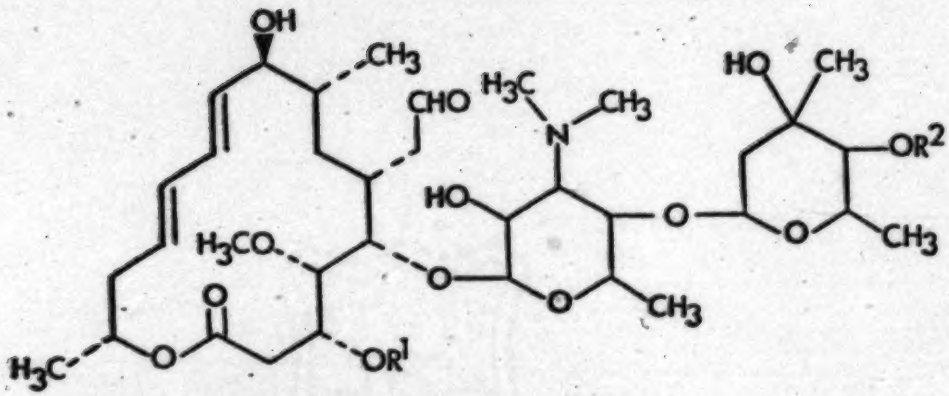
CHAPTER 2: PROPERTIES OF LEUCOMYCIN

The leucomycins and carbomycins (magnamycins) are members of a clinically important class of macrolide antibiotics. These 16-membered ring compounds, of which there are now at least 40, exhibit strong antibacterial activity. More recently, these macrolide antibiotics have been reported to exhibit a high antimycoplasma activity.[47] Furthermore, they generally show greater biological activity than the 14-membered ones.[48] In this chapter, the chemical and biological properties of the 16-membered macrolide antibiotic leucomycin are discussed in some detail.

To date, at least ten leucomycin substrates have been successfully isolated from the fermentation broth of Streptomyces kitasatoensis.[49] The structures of eight of these compounds have been fully elucidated by Ōmura et al.[50] and all ten are shown in Figure 6.

It can be seen from structure 19 that the leucomycins are made up of three moieties: (1) a 16-membered lactone, (2) the sugar mycaminose (3,6-dideoxy-3-dimethylamino-D-glucopyranose), and (3) the sugar mycarose (2,6-dideoxy-3-C-methyl-L-ribohexose). The structural differences involve the presence of either a hydroxyl or O-acetyl group at the C_3 position and the nature of R_2 on mycarose. The hydroxyl group (called the Fr group) is present in leuco-

Figure 6: Structure of Leucomycins



19

			R_1	R_2
Leucomycin	A_1	20	H	$COCH_2CH(CH_3)_2$
	A_3	4	$COCH_3$	$COCH_2CH(CH_3)_2$
	A_4	21	$COCH_3$	$COCH_2CH_2CH_3$
	A_5	22	H	$COCH_2CH_2CH_3$
	A_6	23	$COCH_3$	$COCH_2CH_3$
	A_7	24	H	$COCH_2CH_3$
	A_8	25	$COCH_3$	$COCH_3$
	A_9	26	H	$COCH_3$
	U	27	$COCH_3$	H
	V	28	H	H

mycins A_1, A_5, A_7, and A_9 and the O-acetyl group is present in the A_3, A_4, A_6, and A_8 compounds. The acyl groups on mycarose are isovaleryl (A_1, A_3), butyryl (A_4, A_5), propionyl (A_6, A_7) and acetyl (A_8, A_9).

A) ISOLATION AND STRUCTURE OF LEUCOMYCIN A_3

In the late 1960's, there was much active research directed towards the isolation and determination of the structure of the leucomycins. Some of the resulting information is tabulated in Table 1.[51] This information, together with the ^1H- and ^{13}C-NMR and IR spectral data, led to the final elucidation of the structure of these compounds.

The following paragraphs summarize some of the results of the research and their structural implications.

It was found that separation of the leucomycin complex by chromatography on silicic acid gave a compound, leucomycin A_3 4 as colorless prisms upon crystallization from benzene.[52] From microanalytical data, the molecular formula was determined to be $C_{42}H_{69}O_{15}N$. Although one nitrogen atom was present, negative ninhydrin and Van Slyke nitrogen tests indicated the absence of a primary amine. The Zeisel test showed that one methoxyl group was present while Tollen's and tetrazolium tests were positive.

Table 1: Properties of Carbomycin and Leucomycin

Antibiotic	Producing Organism	mp (°C)	Molecular Formula	$[\alpha]_D$ ($CHCl_3$)	UV λmax
Carbomycin A	St. halstedii	199-200	$C_{42}H_{67}O_{16}N$	-58.6°	
Carbomycin B	St. halstedii	141-144	$C_{42}H_{67}O_{15}N$	-35.0°	
Leucomycin A_1	St. kitasatoensis		$C_{40}H_{67}O_{14}N$	-66.0°	232.0(400)
Leucomycin A_3	St. kitasatoensis	120-121	$C_{42}H_{69}O_{15}N$	-55.4°	231.5(351)
Leucomycin A_4	St. kitasatoensis	126-127	$C_{41}H_{67}O_{15}N$	-50.0°	231.5(375)
Leucomycin A_5	St. kitasatoensis	120-123	$C_{39}H_{65}O_{14}N$	-52.0°	231.5(380)
Leucomycin A_6	St. kitasatoensis	135-137	$C_{40}H_{65}O_{15}N$	-56.0°	231.5(405)
Leucomycin A_7	St. kitasatoensis		$C_{38}H_{63}O_{14}N$	-65.0°	232.0(405)
Leucomycin A_8	St. kitasatoensis	147-149	$C_{39}H_{62}O_{15}N$	-58.3°	232.0(480)
Leucomycin A_9	St. kitasatoensis		$C_{37}H_{61}O_{14}N$	-65.1°	232.0(395)
Leucomycin U	St. kitasatoensis				
Leucomycin V	St. kitasatoensis				

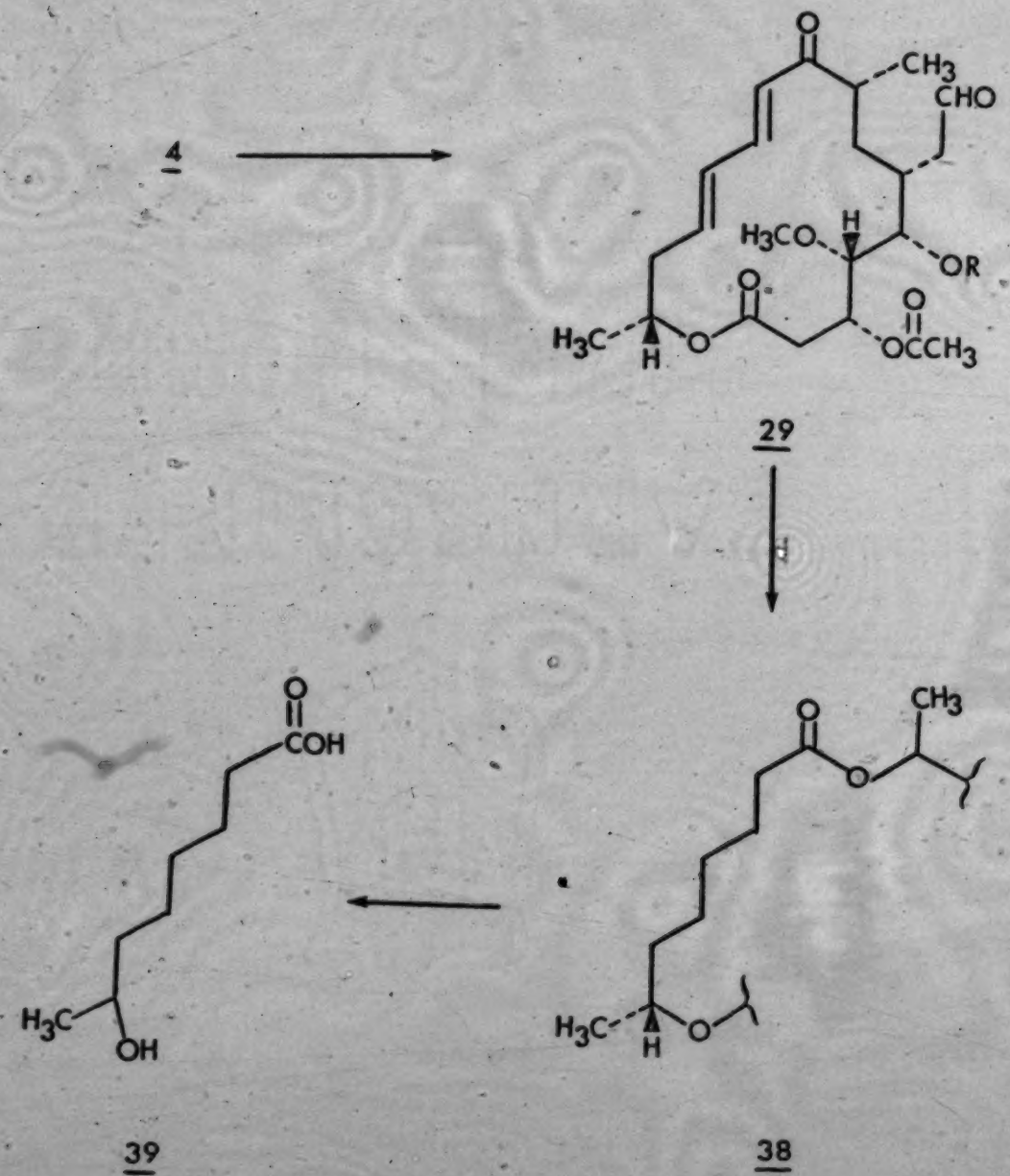
The spectral data of 4 provided valuable structural information. The infrared spectrum exhibited strong peaks at 1728 and 1746 cm^{-1} (carbonyl), 1230 cm^{-1} (acetyl), a weak absorption band at 2725 cm^{-1} (aldehyde) and 1661 cm^{-1} (double bond). The NMR spectrum in $CDCl_3$ suggested the presence of one dimethylamino group (2.49 ppm), one acetyl group (2.22 ppm), four olefinic protons (4H, 5.3-6.7 ppm) and C-methyl groups at ca. 1 ppm.[53] The infrared spectrum of diacetyl leucomycin A_3 still showed a hydroxyl absorption, therefore indicating the presence of a tertiary alcohol.[8] It was also found that the ^{1}H-NMR of the thiosemicarbazone derivative displayed a triplet at 7.62 ppm (J=5 cps, R-CH_2CH=N-) suggesting the presence of a CH_2CHO group. Further, leucomycin A_3 decolorized permanganate and bromine solutions, and during catalytic hydrogenation (5% Pd-C) in ethanol, 2 molar equivalents of hydrogen were absorbed. The ultraviolet absorption spectrum of 4 displayed a strong peak at 231.5mμ (ε 29,100). The position and intensity was characteristic of an $\alpha, \beta, \gamma, \delta$ - unsaturated alcohol or ether.

The fundamental reactions in the structural determination of leucomycin A_3 are illustrated in Figure 7. Alkaline hydrolysis of 4 gave the sodium salts of acetic and isovaleric acids. After oxidation of 4 with activated manganese dioxide, the ultraviolet spectrum of the product

29 indicated the presence of an α, β, γ, δ - unsaturated ketone, λ max 224mμ (ε 6,200) and 279.5mμ (ε 21,900), therefore suggesting an α, β, γ, δ - unsaturated alcohol in 4. Treatment of 4 with dilute hydrochloric acid gave 30 and α,β-isovalerylmycarose 31 and 32, while drastic acid hydrolysis of demycarosyl leucomycin A_3 30 produced α,β-mycaminose 34 and 35. The neutral and basic sugars were found to have the α - and β - configurations respectively as suggested by their ^{1}H-NMR and infrared spectral data. Acetylation of 30 gave diacetate 33 which lacked hydroxyl absorption in the infrared spectrum. Both 30 and its diacetate 33 displayed signals due to three methyl groups in their ^{1}H-NMR spectrum. The nature of the C_{13}-C_{15} segment was determined by treatment of 4 with ozone followed by hydrogen peroxide oxidation to give β-hydroxybutyric acid 36, suggesting the presence of the moiety 37.

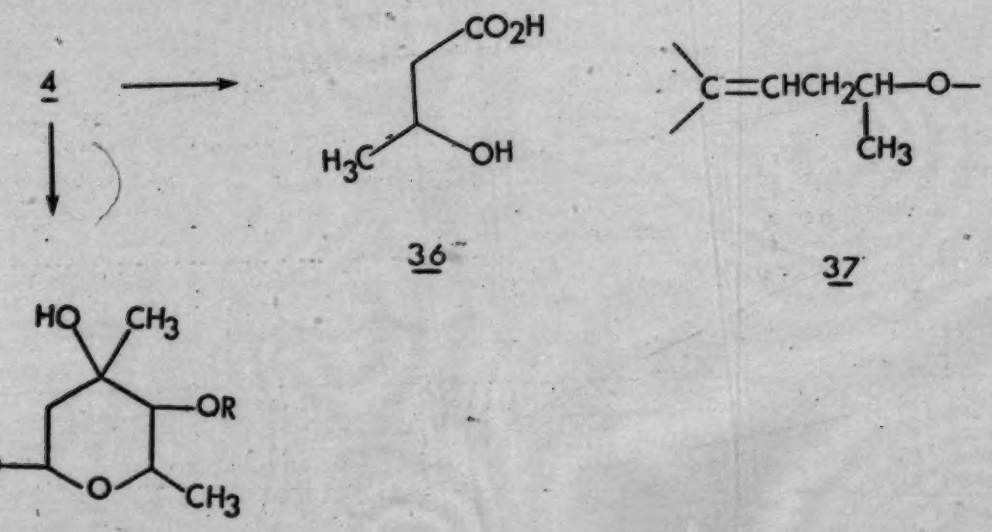
Analysis of the diene portion by ^{1}H-NMR showed a signal at δ 4.05 ppm due to the C_9 signal which shifted to lower field upon acetylation. The C_9 proton exhibited coupling with the C_{10} proton at 5.6 ppm (J=8.9 cps) and the C_8 proton (J=4.2 cps), however, the C_8 signal could not be detected. The signals of the C_{11} proton at δ 6.60 ppm (1H, $J_{11,10}$=15.4 cps, $J_{11,12}$=10.0 cps) and the C_{12} proton at δ 6.05 ppm (1H, $J_{12,11}$=10.0 cps, $J_{12,13}$=15.2 cps) indicated an E, E configuration for the diene system.

Figure 7: Structural Determination of Leucomycin A_3



39 38

Figure 7 (Continued)



36

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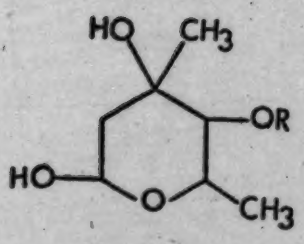


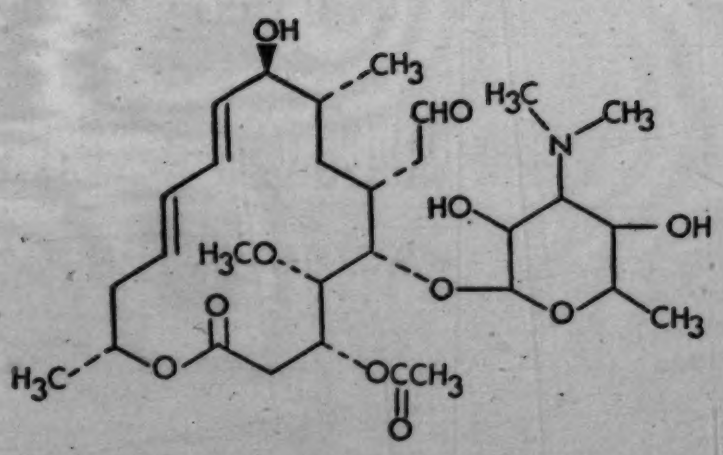
α-31

β-32

OR = Isovaleryl

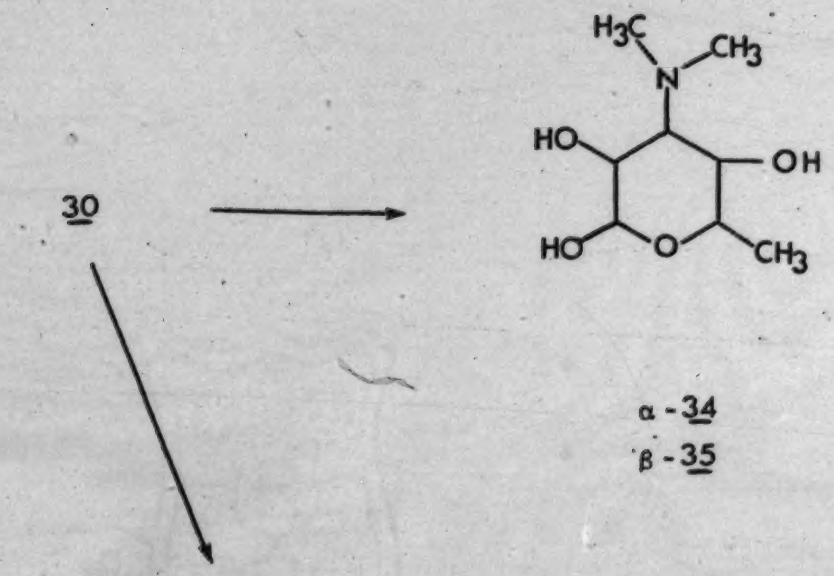
+

47 +

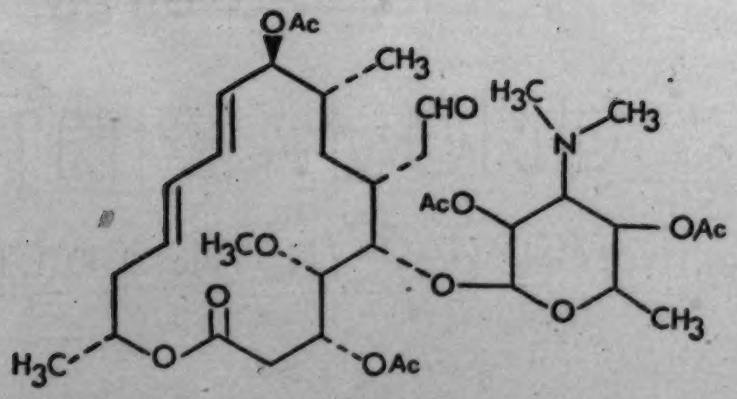


30

Figure 7 (Continued)

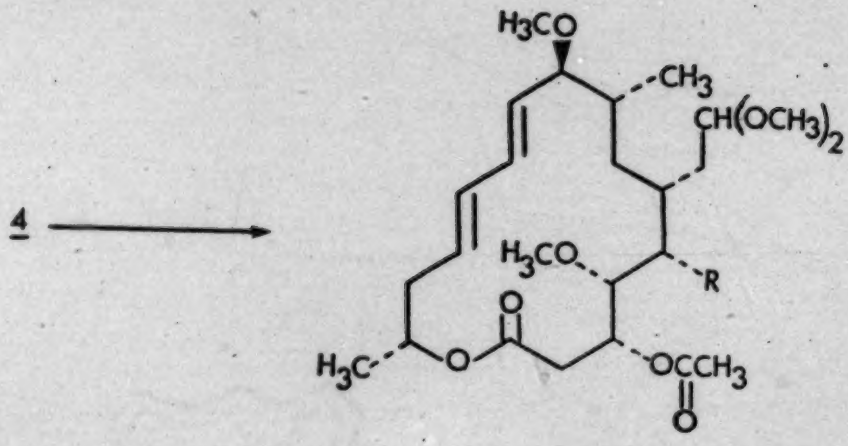


α - 34
β - 35



33

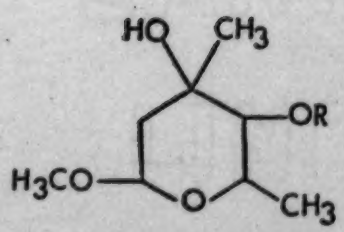
Figure 7 (Continued)



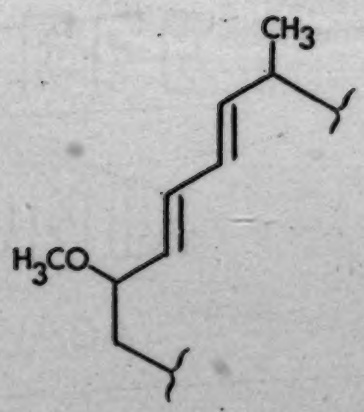
40

R = Mycaminose

+



+



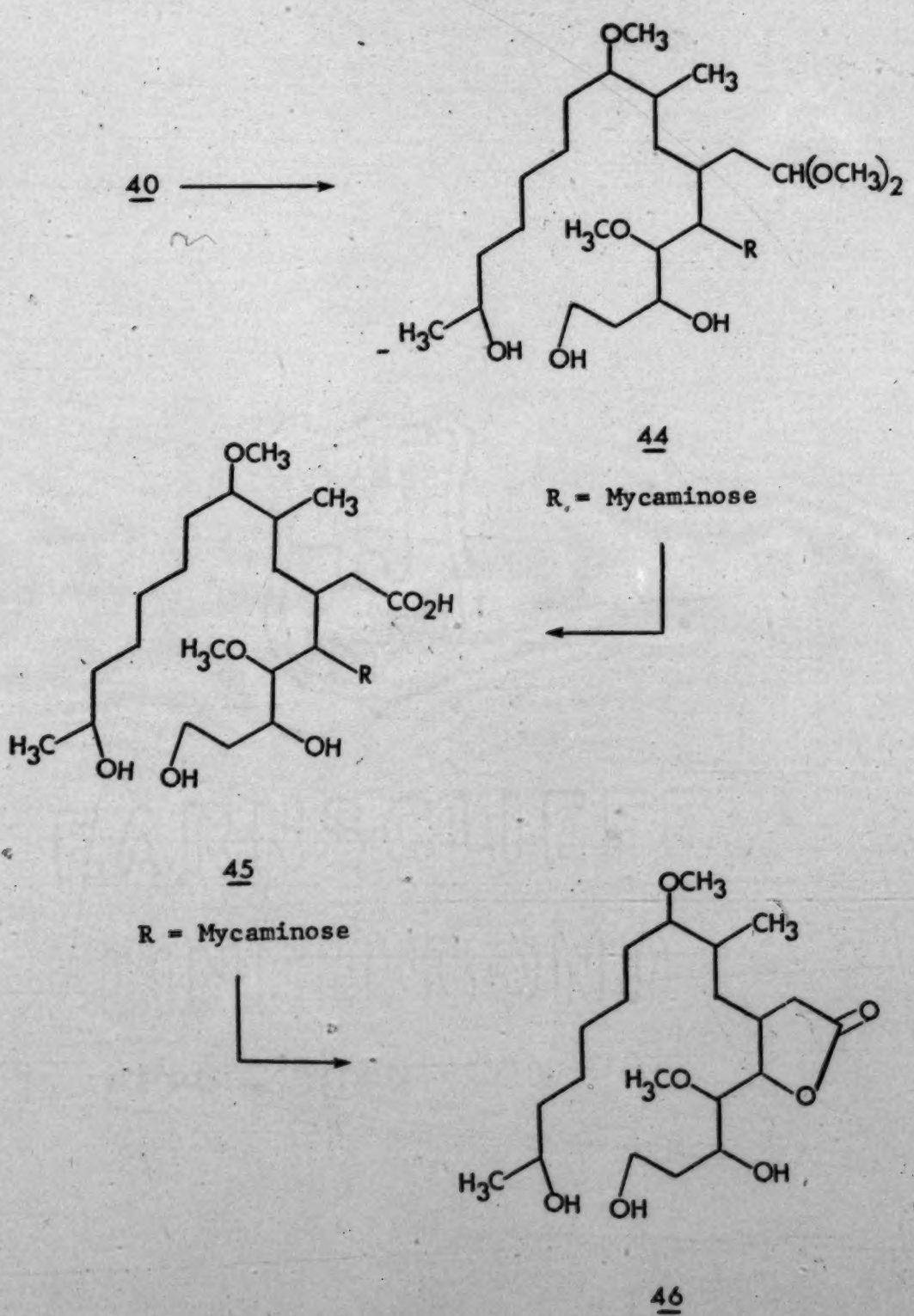
α - 42

β - 43

OR = Isovaleryl

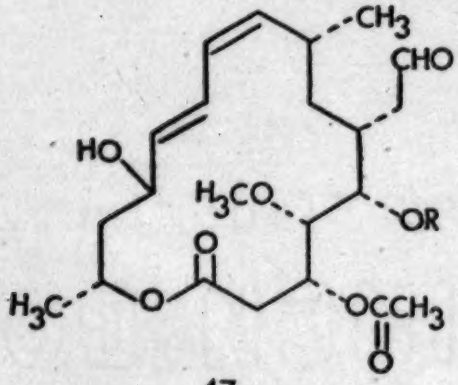
41

Figure 7 (Continued)



The position of the CHO group in the lactone moiety was determined by the method of Woodward.[5a] The aldehyde portion of 4 was first converted to the methyldemycarosyl leucomycin A_3 dimethylacetal 40 by treatment with methanol containing a trace amount (1%) of hydrochloric acid. Two mycarose moieties, 42 and 43, along with re-arrangement product 41 were also isolated from the reaction mixture. Catalytic hydrogenation (5% Pd-c) of 40 gave tetrahydro methyl demycarosyl leucomycin A_3 which was directly reduced with lithium aluminum hydride to the octahydro compound 44. Subsequent liberation of the aldehyde with dilute acid followed by oxidation with hydrogen peroxide gave acid 45. The mycaminose portion could be removed by heating with dilute hydrochloric acid and the resulting product 46 displayed an infrared absorption at 1770 cm^{-1} characteristic of a 5-membered lactone. This sequence implied that the mycaminose was bonded in the position γ to the aldehyde group. It was also found by Ōmura[54] that oxidation of 4 with active manganese dioxide gave 9-dehydro leucomycin A_3 29 which was identical in all respects with the already structurally established carbomycin B. Further structural information was obtained by hydrolysis of leucomycin A_3 4 with hydrochloric acid to give compound 47 which was subsequently converted to the crystalline demycarosyl leucomycin A_3 hydrobromide with an aqueous ethanolic solution of hydrobromic acid. X-ray crystallographic analysis of the hydrobromide indicated that

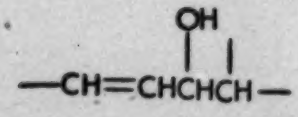
the C_9 hydroxy had undergone re-arrangement, however, the configuration of the rest of the molecule was determined.[55]



47

R = Mycaminose

One remaining problem in the structural determination of 4 concerned the position and absolute configuration of the C_9-hydroxyl group. The ^{1}H-NMR spectrum displayed a double doublet at δ4.05 ppm, consistent with the structure of the segment 47a. In order to confirm the presence of the



47a

hydroxyl group in the 9-position, the 9-dehydro leucomycin A_3 29 was hydrogenated (5% Pd-c) and subjected to Baeyer-Villiger oxidation with perbenzoic acid to give 38 shown in Figure 7. Finally, alkaline hydrolysis gave compound 39 which was identical in all respects to 7-hydroxyoctanoic acid. The absolute configuration of the C-9 position was later determined to be the R configuration.[56]

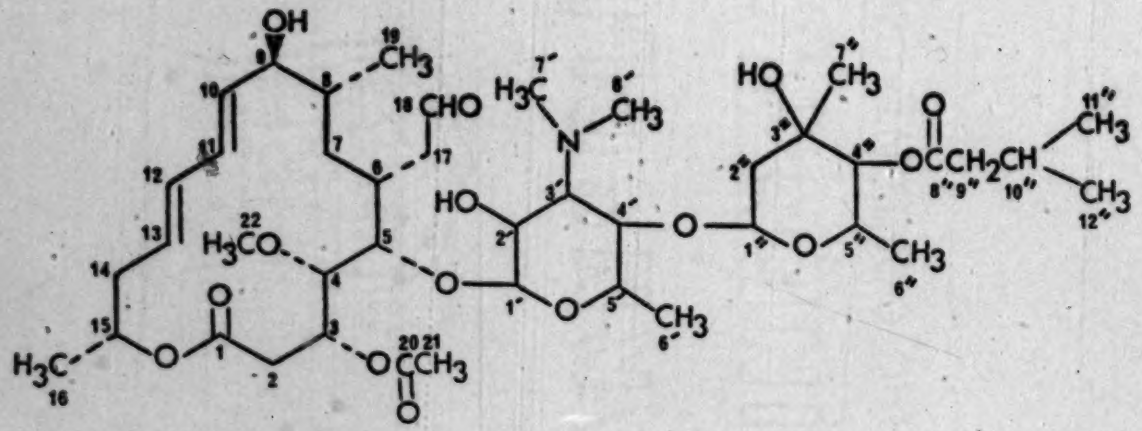
To complete the structural data of 4, the ^{13}C-NMR spectrum is tabulated in Table 2. The low field signal at δ201.2 is due to the aldehyde carbon, and the lactone carbonyl, the C_3-acetyl and the isovaleryl carbonyl all appear at around δ 170. The signals at δ 127-136 were assigned to the four olefinic carbons C_{10}-C_{13}, and the signals at δ 103.7 and 97.0 to the β-anomeric carbon of mycaminose and the α-anomeric carbon of mycarose respectively.[57]

These results basically completed the first stage of structural studies of leucomycin A_3.

B) CONFORMATION

As was mentioned in Chapter 1, conformational analysis of macrolides in solution is an important factor in the examination of their structure-activity correlation as well as their chemical reactivity. The conformation of

Table 2: ^{13}C-NMR of Leucomycin A_3 4



4

Table 2 (Continued)

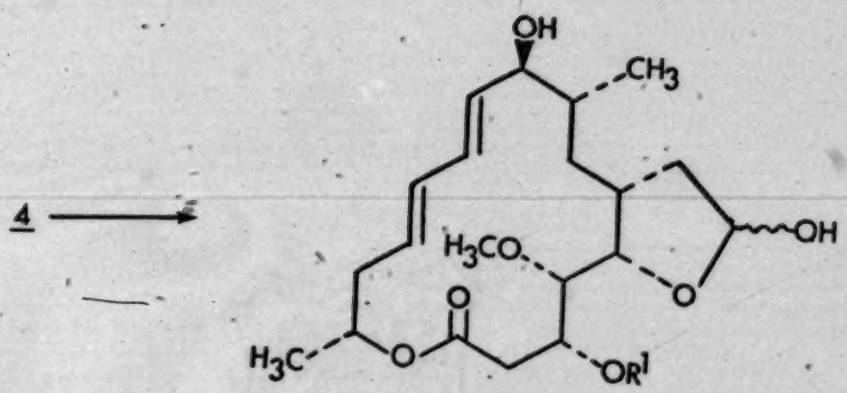
Aglycone				Mycaminose		Mycarose	
C-1	169.9 ppm	C-13	132.1 ppm	C-1'	103.7 ppm	C-1''	97.0 ppm
C-2	37.0	C-14	40.9 (c)	C-2'	69.0 (d)	C-2''	41.9
C-3	71.9	C-15	68.8 (d)	C-3'	69.0 (d)	C-3''	69.3
C-4	77.5	C-16	20.3	C-4'	76.0	C-4''	77.1
C-5	84.9	C-17	42.4 (c)	C-5'	72.9	C-5''	63.5
C-6	28.8 (a)	C-18	201.2	C-6'	18.8 (e)	C-6''	17.8 (e)
C-7	30.4 (a)	C-19	14.7	C-7'	41.9	C-7''	25.5
C-8	33.5	C-20	170.8	C-8'	41.9	C-8''	172.9
C-9	73.1	C-21	21.3			C-9''	43.3
C-10	135.7 (b)	C-22	62.4			C-10''	25.5
C-11	127.6 (b)					C-11''	22.4
C-12	132.6 (b)					C-12''	22.4

Assignments (a), (b), (c), (d) and (e) may be reversed.

erythromycin had been determined to be quite rigid. From the infrared, CD and ^{1}H-NMR spectral data, the aglycone portion of leucomycin seems to have a flexible conformation.[58,59] The CD measurements in various solvents and under variable temperatures have shown that the ester-carbonyl region is extremely mobile. From ^{1}H-NMR data, it has been observed that the aldehyde group, the C_3-acetyl group and the C_{11}-proton are all in close proximity above the lactone ring. The high mobility of leucomycin may arise from the absence of the conformational stabilization by the many methyl groups found in erythromycin.

C) ISOLATION OF THE AGLYCONE

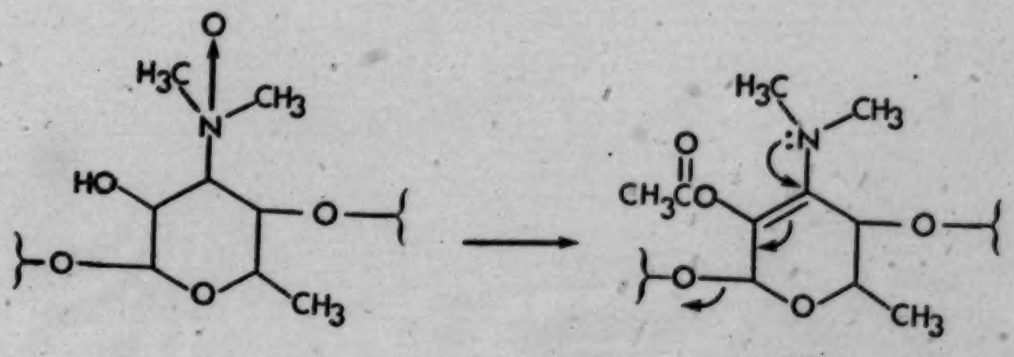
Important in the structural and biosynthetic studies on macrolides is the isolation of the lactone. Initial attempts to cleave the disaccharide unit with mild acid treatment failed due to the stability of the antibiotic and more drastic conditions caused decomposition of the lactone. An efficient method for the removal of the sugars has been the modified Polonovski reaction.[60] The N-oxide of 4 was prepared in high yield by reaction with m-chloroperbenzoic acid in chloroform. The structure was confirmed from the ^{1}H-NMR spectrum by the shift to lower field of the N-methyl signal from δ 2.6 in the amine to δ 3.35 in the N-oxide. Refluxing of the N-oxide with acetic acid in chloroform gave the desired aglycone 48.



48

$R^1 = COCH_3$

Girota and Wendler, in a later publication,[61] reported the preparation of 48 by treatment of the N-oxide of 4 with acetic anhydride and pyridine. Their results were apparently similar to that obtained by Ōmura, however, they also isolated a second product, an enamine 49 which was formed by introduction of a double bond between the 2' and 3' positions of the mycaminose moiety. The enamine was readily converted to 48.



49

48

D) BIOSYNTHESIS

In contrast to the structural elucidation which is now virtually complete, the biosynthesis of the leucomycins still remains to be fully determined. Early work on the biosynthesis of magnamycin revealed that the sugars, mycaminose and mycarose, originate from glucose.[62] These studies also showed that the N-methyl of mycaminose and the O-methyl in the lactone originate from the S-methyl group of methionine and that the isovaleryl group on mycarose has L-leucine as its precursor. The origin of the lactone ring carbons was determined from ^{13}C-NMR spectral studies using the ^{13}C enriched precursors [1-^{13}C]-acetate, [2-^{13}C]-acetate,

[1-^{13}C]-butyrate and [1,4-$^{13}C_2$]-succinate.[63] Feeding experiments were carried out with Streptomyces kitasatoensis. Enhancement in peak heights of the proton-decoupled ^{13}C-NMR spectra were obtained, however, relative intensities could only be estimated due to interference by a Nuclear Overhauser effect.

The results of the feeding experiments indicated no incorporation of [1,4-$^{13}C_2$]-succinate.[64] Relative peak heights of the [^{13}C]-acetate labelled samples indicated that carbons -1, -5, -9, -11, -13, -15, -17 and -20 originate from the C-1 of acetate (the incorporation at carbons -5 and -17 being much weaker), and that carbons -2, -6, -7, -8, -10, -12, -14, -16, -18, -19 and -21 originate from C-2 of acetate (the enrichment at carbon -6 again much weaker). These results were confirmed by labelling experiments with [1,2-$^{13}C_2$]-acetate. The proton-noise decoupled ^{13}C-NMR spectrum revealed that carbons -1, -2, -9 to -16, -20 and -21 were enriched and that each of the signals was accompanied by a doublet arising from vicinal ^{13}C-^{13}C coupling ($J_{C_1-C_2}$=63.2 Hz, $J_{C_9-C_{10}}$=51.0 Hz, $J_{C_{11}-C_{12}}$=59.8 Hz, $J_{C_{13}-C_{14}}$=45.3 Hz, $J_{C_{15}-C_{16}}$=38.7 Hz and $J_{C_{20}-C_{21}}$=64.1 Hz). Only singlets were observed for carbons -8 and -19. The weak enrichment at these sites was due to indirect incorporation, indicating that carbons -1, -2, -9 to -16, -20 and -21 were directly derived from intact acetate. In the sample derived from [1-^{13}C]-propionate, only carbon -7 was specifically

enriched. This suggested that carbons -7, -8 and -19 arose directly from propionate.[65] The carbons -5, -6, -17 and -18 were negligibly enriched by [^{13}C] acetates, inferring that they are only indirectly derived from acetate. Feeding experiments with [1-^{13}C]-butyric acid and [1'-^{13}C]-ethylmalonic acid were carried out. The results showed enrichment at centers -5 and -17 from [1-^{13}C]-butyric acid and[1'-^{13}C]-ethylmalonic acid respectively, supporting the fact that carbons -5, -6, -17 and -18 were derived from butyrate.

The method of incorporation of butyrate should be similar to that of acetate and propionate. For example, secondary metabolites containing acetate and propionate units are possibly synthesized via the same process as fatty acids, that is, acetyl-CoA and propionyl-CoA function as initiators while malonyl-CoA and methyl-CoA participate in chain extension.[66] In the same manner, ethylmalonic acid should be incorporated in the form of ethylmalonyl-CoA as an actual participant of a butyrate unit in chain extension.

In the samples obtained by feeding [1-^{13}C]-butyrates, only carbon -5 was highly enriched with negligible incorporation in carbons -1, -9, -11, -13, -15 and -20 which should originate from C-1 of acetate. Possibly this arose from the conversion of butyrate into acetate by β-oxidation. Carbon -7 also exhibited definite enrichment from [1-^{13}C] labelled butyrate. This enrichment may arise from conversion of the [1-^{13}C]-butyrate into succinate by ω-oxidation, fur-

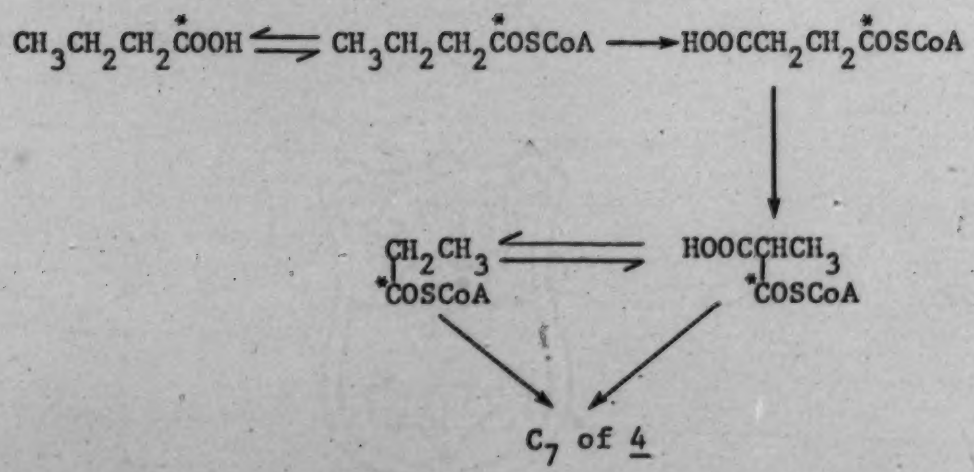
ther isomerization to methylmalonyl-CoA via succinyl-CoA and finally, incorporation into the aglycone of 4 as shown in Figure 8.

No enrichment on carbons -3 and -4 was observed by feeding experiments with [1-^{13}C]-glycine, diethyl [1-^{13}C]-oxalate, [2-^{13}C]-malonic acid, and diethyl [1,4-$^{13}C_2$]-succinate, indicating these two carbons may arise from a different source. In summary, the aglycone of 4 originates from five acetates, one propionate, one butyrate and an unknown precursor for carbons -3 and -4.

E) BIOLOGICAL ACTIVITY

As a result of the many biological studies on the leucomycins, several clinically useful properties of these macrolides were found. For example, leucomycins A_1-A_9 were found to effectively inhibit the growth of gram-positive bacteria and gram-negative coccus, but not of gram-negative bacilli.[67] It was also found that an increase in antibacterial activity of both the Fr and Ac groups was related to an increase in the length of the carbon chain R_2 with the isovaleryl group having the highest activity. The antibacterial activity was higher for the Fr group than the Ac group, however, the latter showed higher blood level and lower toxicity than the Fr group. The blood level of the 16-membered macrolides is known to be lower than that of

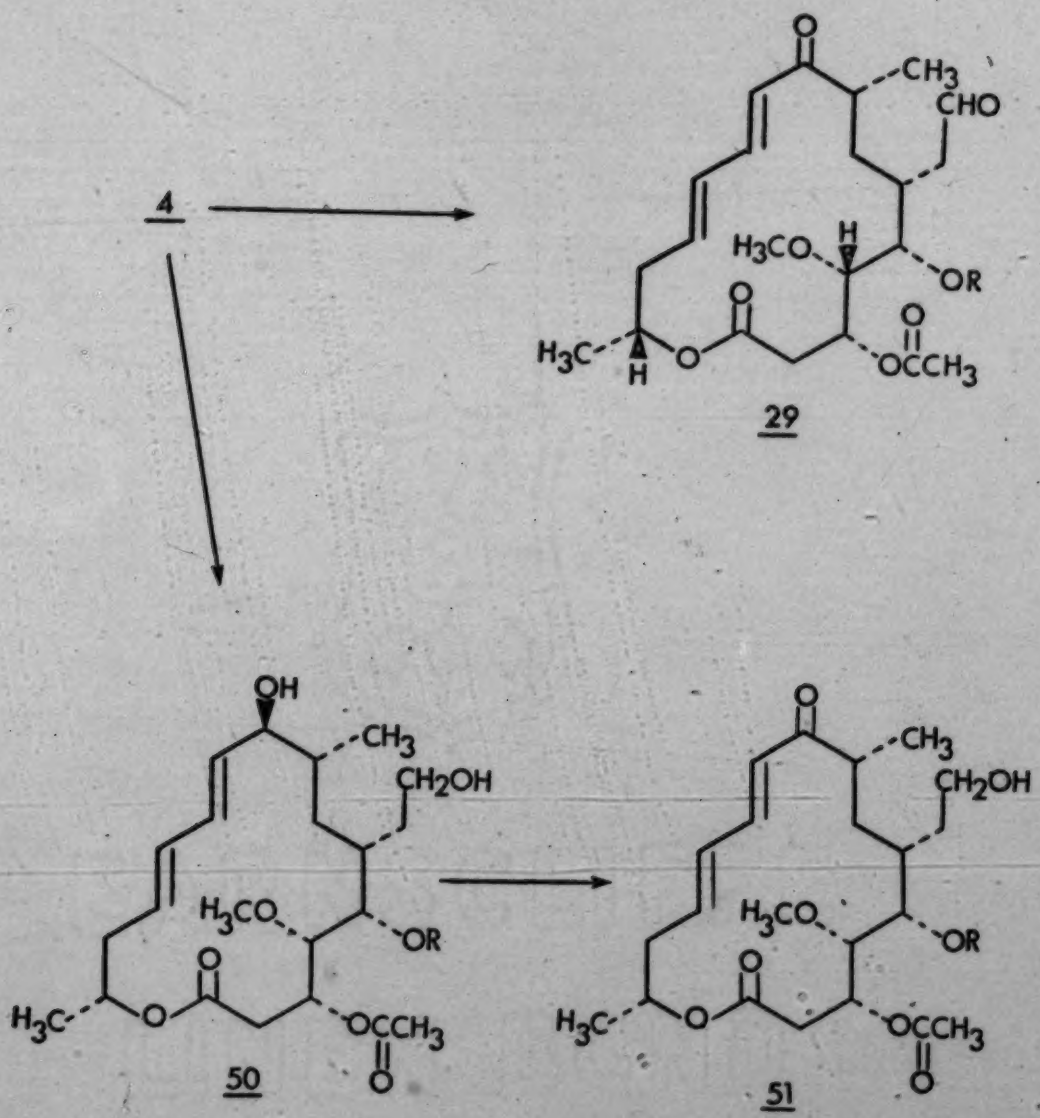
Figure 8: Enrichment of C_7



the 14-membered antibiotics, but this problem has been partially overcome by acylation.[48] The methodology available for acylation is described later in this section.

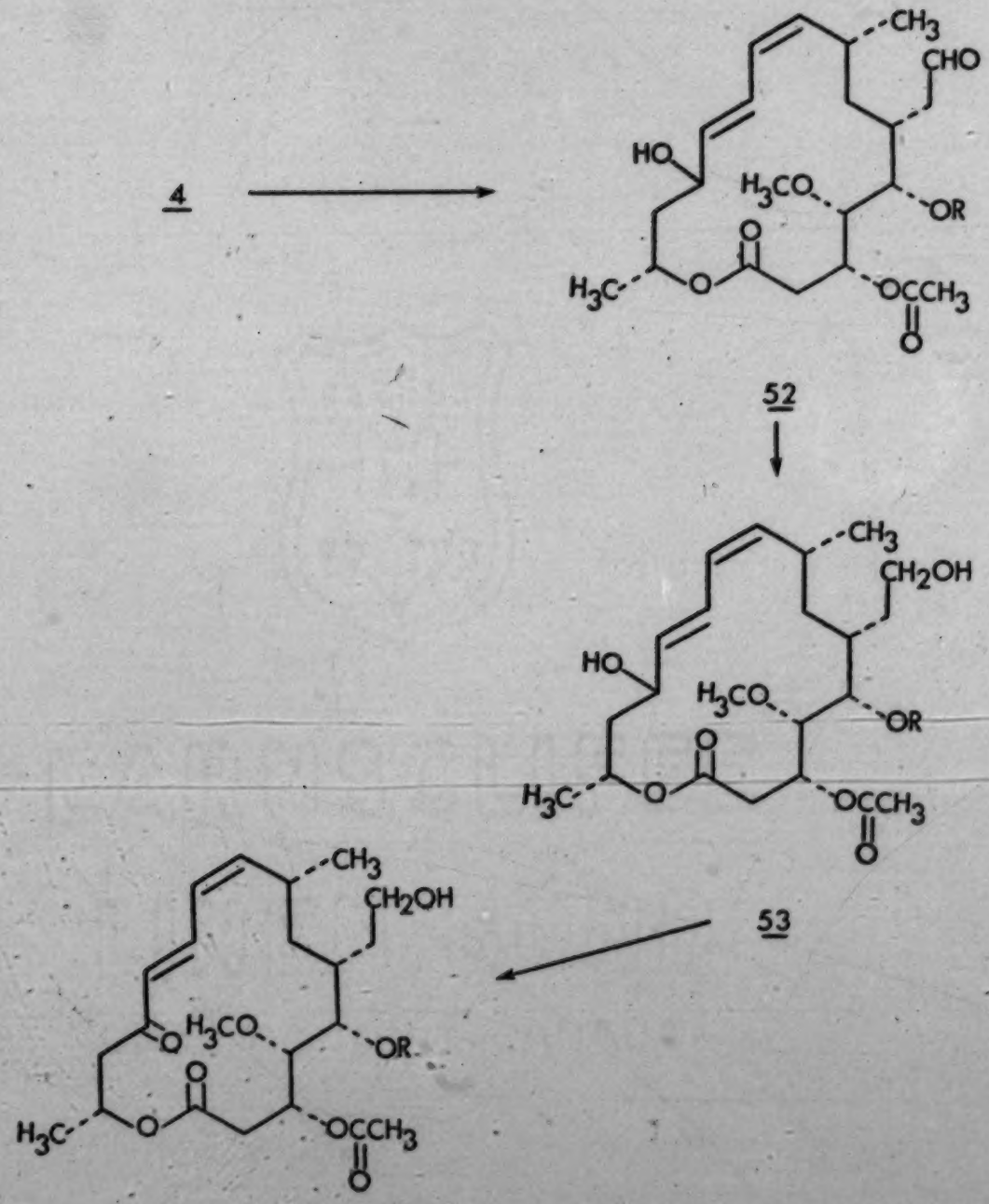
The α, β, γ, δ-unsaturated alcohol moiety was not found to be related to antibacterial activity, but modification of the aldehyde group strongly affected such activity. Either chemical reduction of the aldehyde to an alcohol or conversion to the thiosemicarbazone resulted in significant reduction of antibacterial activity. To determine the effect of structural modifications of these moieties towards antibacterial activity, compounds 50 to 55 were prepared as follows. Oxidation of leucomycin A_3 4 with manganese dioxide in chloroform gave unsaturated ketone 29. Reduction of 4 with ethanolic sodium borohydride gave diol 50 which was subsequently oxidized (MnO_2 in chloroform) to α, β, γ, δ-unsaturated ketone 51. Re-arrangement of the C_9 hydroxy group could be effected by treatment with aqueous 0.2 N hydrochloric acid at 60° for two hours to give isoleucomycin A_3 52 which upon subsequent sodium borohydride reduction in ethanol gave diol 53. Oxidation of diol 53, as before, gave re-arranged α, β, γ, δ-unsaturated ketone 54. These reaction sequences are illustrated in Figure 9. The effect of modification of the formyl and the 9-hydroxyl group is summarized in Table 3. This data reveals the important contribution of the formyl group or, in its place, a carbonyl at the 9-position towards antibacterial activity. From the

Figure 9: Synthesis of Leucomycin Derivatives.



R = Sugars

Figure 9 (Continued)



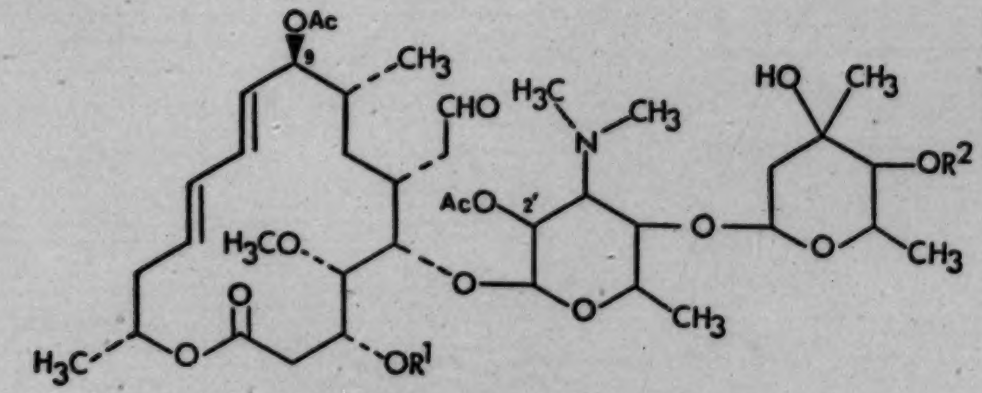
R = Sugars

Table 3: Antimicrobial Activity of Leucomycin Derivatives

Test Organisms		Minimum Inhibitory Concentration g/ml						
		4	29	50	51	52	53	54
Bacillus subtilis	PCI 219	0.2	0.4	>100	25	0.05	>100	50
Staphylococcus aureus	FDA 209P	0.4	0.4	> 100	25	0.05	> 100	100
Sarcina lutea	PCI 1001	0.5	0.05	100	1.56	0.05	> 100	6.25
Mycoplasma hominis type IC		<0.20	-	>100	1.56	<0.20	100	25

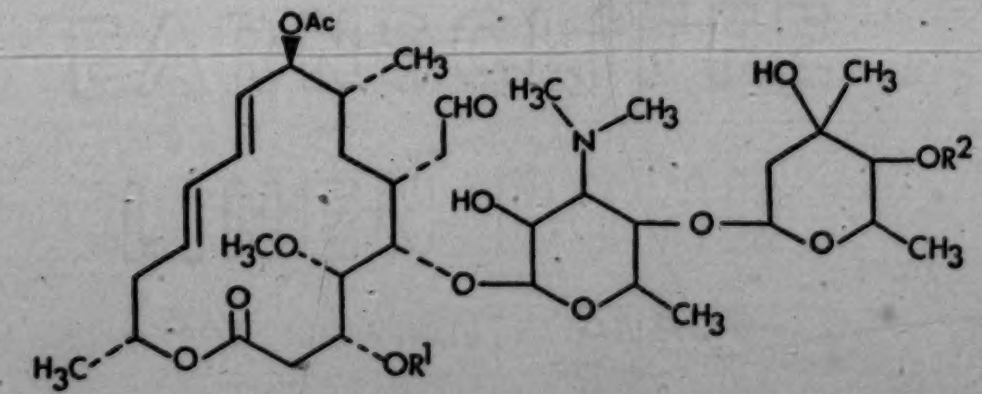
results in Table 3, it can also be seen that isomerization of the 9-hydroxy compound to the 13-hydroxy compound by allyl re-arrangement in acid (pH 2.5-3.8)[67] causes only a slight decrease in antibacterial activity.

Attempts have been made to try to improve the biological activity of 16-membered macrolides. For example, it is known that they generally exhibit lower blood level concentration than the 14-membered antibiotics. As was mentioned earlier, acylation (specifically at the C_9-hydroxyl) increased the blood level of the 16-membered macrolides. Specific acylation at the C_9-hydroxyl may at first seem difficult since a hydroxyl is present in the 3, 9, 2', 3'' and 4'' positions, however, two effective methods for specific C_9-hydroxyl acylation have been reported.[50,68] One method for achieving this specificity involves treatment of 4 with acetic anhydride in pyridine to give diacetate 55a followed by solvolysis in methanol to give acetate 55. The second method involves selective acylation of the C_9-hydroxyl by reaction of 4 with acetyl chloride in the presence of amine. Acylation of the C_9-hydroxyl resulted in an increased blood level of the antibiotic without changes in its antibacterial activity. To date, there have been no examples of new compounds with good antimicrobial activity resulting from modification of the 3° alcohol at the 3'' position.


OAc
9
CH3
CHO
H3C
N
CH3
HO
CH3
OR2
AcO
2'
O
H3CO
O
O
O
CH3
CH3
O
H3C
O
OR1

55a

4


OAc
CH3
CHO
H3C
N
CH3
HO
CH3
OR2
HO
O
H3CO
O
O
O
CH3
CH3
O
H3C
O
OR1

55

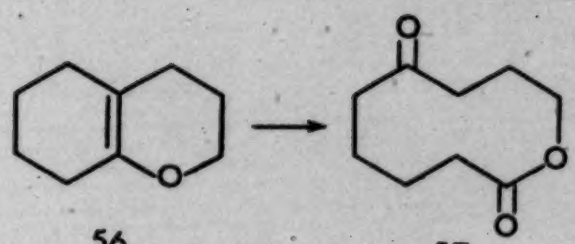
Another important aspect of biological activity is activity towards mycoplasma. In this regard, leucomycin A_3 showed the highest activity. As was mentioned earlier, antibiotics with the Fr group exhibited higher antibacterial activities than those with the Ac group. On the other hand, tests for antimycoplasma showed the antibiotics with the Ac group were more active than the Fr moiety. This reversal of activity is thought to arise from the difference in membrane structure between the two kinds of micro-organisms. It is known that mycoplasma has no cell wall, being enveloped only with a cell membrane.[69]

CHAPTER 3: GENERAL STRATEGY TOWARD MACROLIDE SYNTHESIS

The macrolide antibiotics have been a source of many challenging problems to synthetic organic chemists. As a result, several new synthetic methods for macrolide formation have been developed. This chapter presents a brief summary of some of these methods.

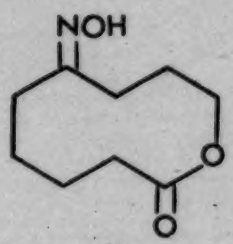
There are two main problems associated with the synthesis of macrolides. One is the construction of medium or large-size lactones. The second problem involves the introduction of chiral centers into a straight chain aliphatic acid.

There are two general methods for the construction of medium or large-size lactone rings. The first method involves breaking of internal bonds in polycyclic systems. An example of this type of approach is cleavage of the bond common to the two rings of a fused bicyclic compound. When the fusion bond is the double bond of a vinyl ether, oxidative cleavage has been used with good results. Thus, Borowitz found that oxidation of vinyl ether 56 with excess m-chloroperbenzoic acid provided ketolactone 57 in satisfactory yields.[70] Similarly, Mahajan[71] reported formation of 58 by reaction of 56 with n-butyl nitrite. Subsequent oxidation of the oximino lactone gave 57. Use of the Borowitz procedure to form 12-membered ketolactones required preparation of vinyl ether 60. This could be accomplished



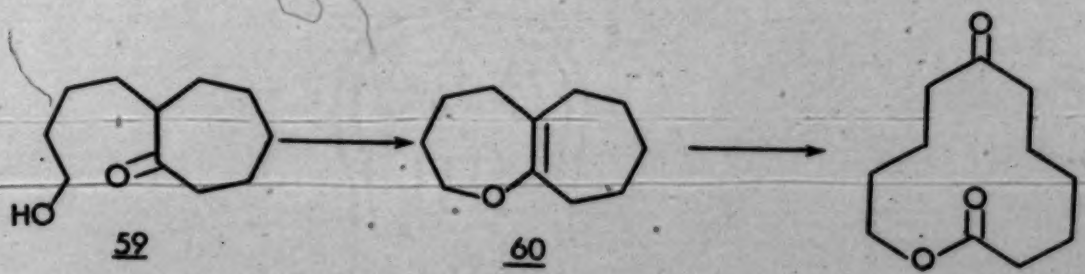
56

57

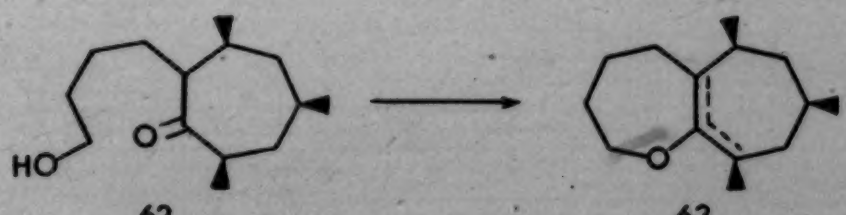


58

in good yields by acid catalyzed dehydration of 59. Oxidative cleavage of 60 gave 61 in 72% yield.[72] However, cyclization of 62, a model compound stereochemically more complicated than 60, gave a mixture of isomeric enol ethers 63 and the reaction proceeded in poor yield.[73] Cleavage of the

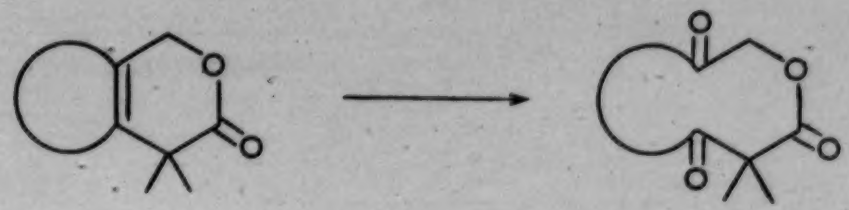


59 60 61



62 63

non-activated fusion-bond in the bicyclic olefin 64 with ozone or potassium dichromate, gave diketolactone 65[74] in 50 to 62% yield.



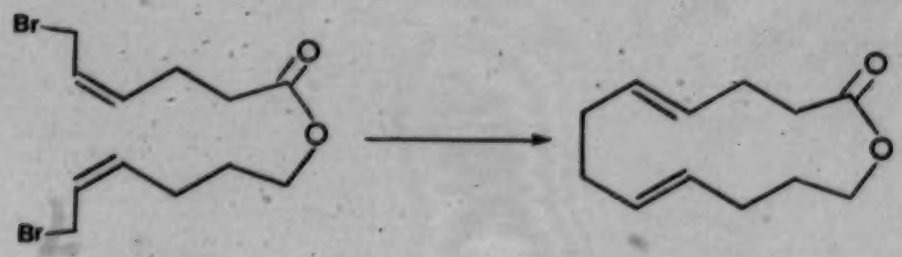
64 65

An interesting example of cleavage of the fusion-bond involves an intramolecular retro-Dieckmann reaction. For example, treatment of 66 with sodium hydride gave 67 in 55% yield.[75]

66 67

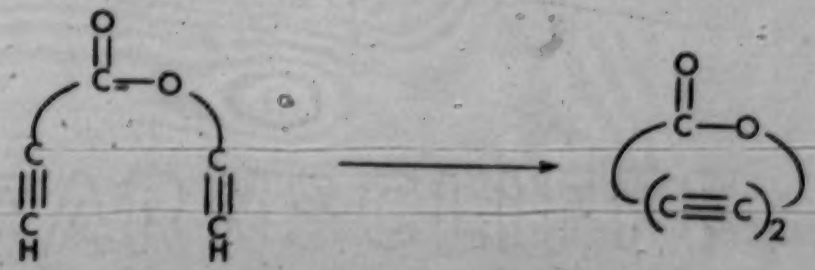
The second method for ring construction involves cyclization of an acyclic precursor. Ring closure, however, is disfavored due to the loss in entropy that accompanies cyclization. Also intermolecular rather than intramolecular reactions often complicate matters. Despite these difficulties, this approach seems to be the most general one.

One of the first examples of this method involved the cyclization of allylic dibromide 68 with nickel carbonyl[76] from which lactone 69 was obtained in 70 to 75% yield.



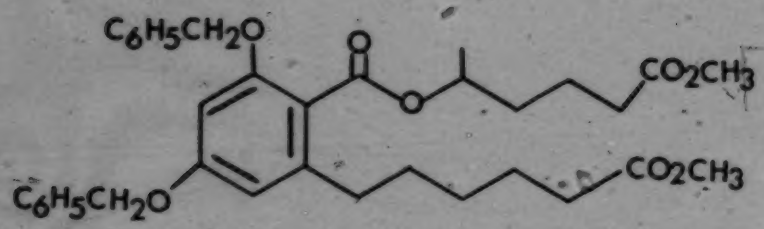
68 69

Lactones have also been synthesized from ω,ω′-diacetylenic esters. Thus, oxidative coupling of 70 with cupric ion gave the corresponding diynolides 71 in high yield.[77]

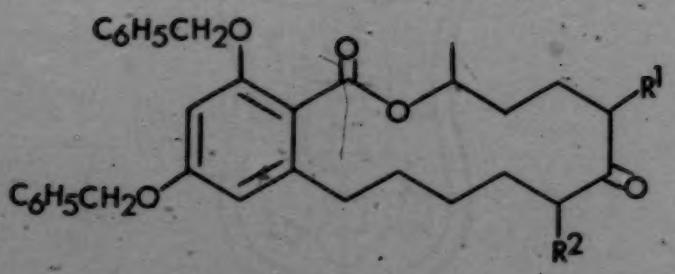


70 71

In another example of this type of approach, an internal Dieckmann condensation has been used to yield derivatives of zearalenone. When triester 72 was treated with sodium bis(trimethylsilyl)amide in refluxing ether, compounds 73 and 74 were formed in 77% yield.[20]



72



73 $R^1 = H$, $R^2 = CO_2CH_3$

74 $R^1 = CO_2CH_3$, $R^2 = H$

A slightly different approach from the previous two-ring construction methods involves direct lactonization of a cyclic ketone by Baeyer-Villiger oxidation. This approach can be useful if the macrocyclic ketone is readily available. Synthesis of such a ketone would have to be carried out under virtually neutral conditions to prevent epimerization at centers adjacent to the carbonyl function.

Thus, preservation of stereochemical integrity in a cyclic ketone may even be a more difficult problem than synthesis of the lactone itself. This approach is further complicated in that for the case of an unsymmetric ketone, two lactonic products are possible, thus making this approach very unattractive.

Of all the macrolide ring formation reactions, lactonization of hydroxy-acids appears to be the most direct and general approach. Therefore, if one adopts this methodology, it is of prime importance to know if the "seco-acid" corresponding to a natural macrolide can be lactonized. In this respect, Stolls' classical work on intra- versus intermolecular esterification of straight chain ω-hydroxyacids[78] was particularly discouraging. He showed that intermolecular bond formation was favored over intramolecular cyclization. However, this lactonization approach is especially appealing since the biosynthetic pathway very likely involves lactonization as the final step. Furthermore, lactonization of the seco-acid as a final synthetic step greatly simplifies the introduction of the appropriate stereochemistry.

With respect to the intra- versus inter-molecular cyclization, it has been found possible to control the outcome of the lactonization reaction providing the chain is long and conformationally flexible. The most common way to promote intramolecular reaction is to employ the high dilution technique. This can be accomplished in practice

by slow addition of the reactant so that reaction of the first portion is virtually complete before introduction of the subsequent portion. Excellent yields have been obtained using this methodology.[79]

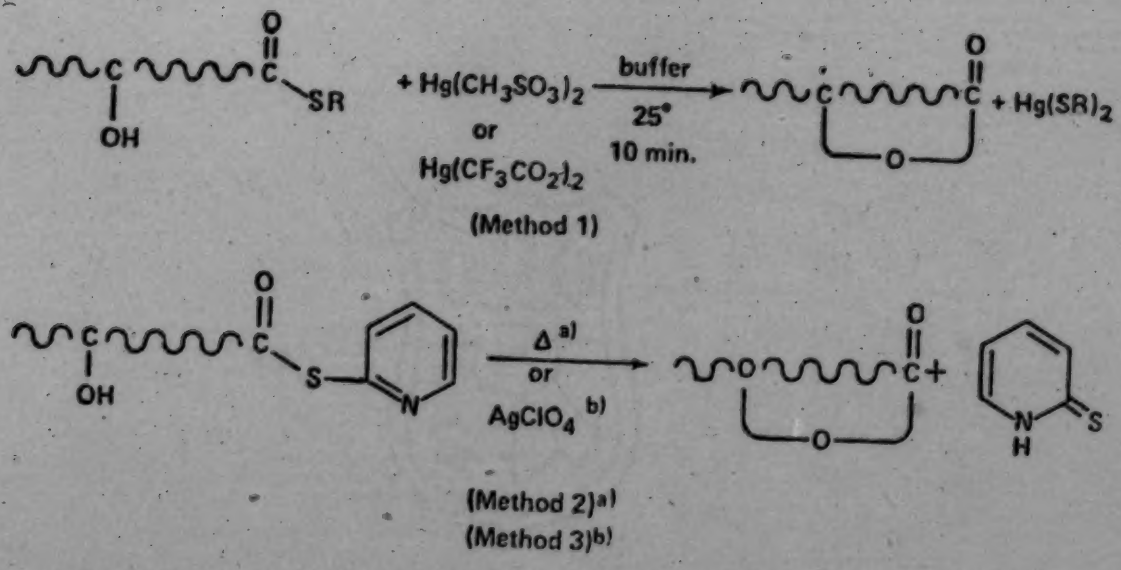
Another serious consideration arises from the steric effect of the numerous substituents toward seco-acid cyclization. It may be recalled from the first chapter that many of the "polyoxo" macrolides are conformationally quite rigid. That this rigidity is passed on to their seco-acids is confirmed by inspection of CPK models. This implies that rotational freedom of most of the C-C bonds is restricted - a condition that favors intramolecular cyclization. Activation of one or both of the interacting moieties of the seco-acid should further enhance intramolecular reaction.

There are now at least three efficient methods available for the formation of the lactone. The first one relies on activation of a hydroxycarboxylic thiol ester with a thiophilic, soft metal ion such as Hg. Application of this method has resulted in the high yield (90%) lactonization of the seco-acid derivatives of zearalenone.[80] The second method, Corey's "double activation" technique,[81] is patterned after Mukaiyama's peptide formation.[82] This method involves refluxing a dilute solution of the thiol ester shown in Figure 10 in a high boiling inert solvent such as xylene or toluene. Modification of this approach constitutes method

three. It was reported by Gerlach[83] that $AgClO_4$ accelerates the reaction so that cyclization can be attained in one hour at room temperature.

With the development of these three techniques, the formation of medium and large-sized lactones can now be satisfactorily accomplished. The second problem, involving introduction of chiral centers into a straight chain aliphatic acid still presents a major synthetic challenge and requires creative and imaginative solutions. The remainder of this thesis is directed towards a solution to this problem.

Figure 10: Lactonization Procedures



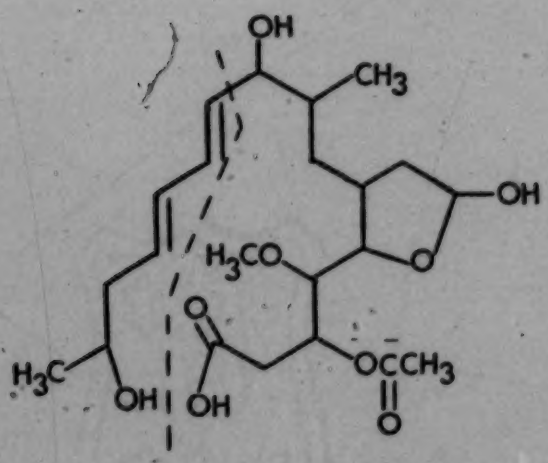
CHAPTER 4: SYNTHESIS OF THE C_1-C_9 AND C_{11}-C_{15} SEGMENTS OF THE AGLYCONE OF LEUCOMYCIN A_3

Recently, we have witnessed the total synthesis of methymycin[14] and erythronolides A and B.[18] The 16-membered macrolide antibiotics thus far have received little or no synthetic attention. To date, the synthesis of leucomycin A_3 has not been reported.[128] Towards this end, the synthesis of both the right hand C_1-C_9 and left hand C_{11}-C_{15} segments of the aglycone of leucomycin A_3 are described in this chapter.

In the preceding chapter, it was shown that the most direct approach to macrolide synthesis involves final lactonization of the seco-acid formally derived from the antibiotic. A reasonable retrosynthesis appears to dissect the seco-acid into the two fragments shown in Figure 11.

Isomers must be combined for the synthesis of the macrolide. Three possible approaches are available; (1) Both segments can be resolved or asymetrically synthesized and combined; (2) One segment can be resolved and used as a resolving agent for the other; or (3) The stereochemical information can be directly transmitted from one segment to the other via chemical reactions, as is achieved in enzymatic reactions. The method to be pursued in the synthesis of leuconolide is the second one. This approach has already

Figure 11: Retrosynthesis of the Seco-Acid

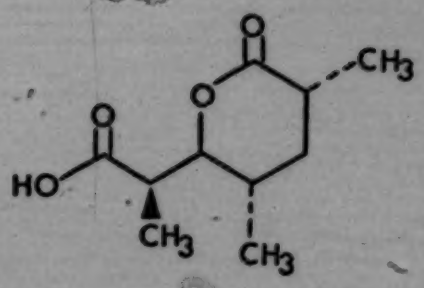


resulted in the successful completion of the synthesis of methymycin.[84] It was hoped, then, condensation of optically pure segment A (C_{11}-C_{15}) and racemic segment B (C_1-C_9) would lead to the proper aglycone. The synthesis of the optically pure C_{11}-C_{15} segment will be described later in this chapter.

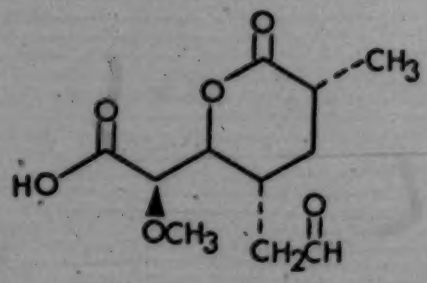
A) SYNTHETIC APPROACH TOWARD THE C_1-C_9 SEGMENT

The design which was used in the partial synthesis of leuconolide, described in this thesis, required the synthesis of two units, the C_1-C_9 segment and the C_{11}-C_{15} segment. The approach adopted towards the synthesis of the C_1-C_9 segment involved use of a lactonic acid intermediate. In the total synthesis of methymycin, the Djerassi-Prelog lactonic acid (shown in Figure 12) was equivalent to the right hand side of the target molecule. This intermediate was useful since it contained all of the appropriate asymmetric carbons for the C_1-C_7 portion of this macrolide antibiotic. Djerassi had reported that this lactonic acid was a degradation product of methynolide[85] and picronolide. Obviously, use of this type of intermediate would lead to a synthetic approach applicable to other macrolides, providing the proper modifications could be made. The corresponding lactonic acid intermediate shown in Figure 12 has not been reported as a degradation product of leuconolide. This

Figure 12: Lactonic Acid Intermediates

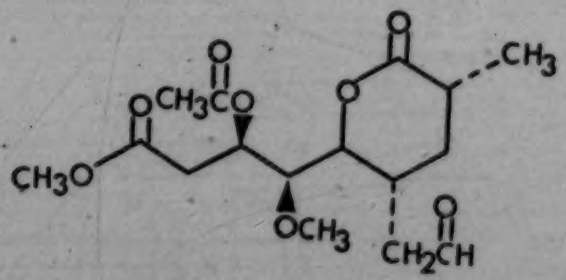


Djerassi-Prelog
lactonic acid



Intermediate for
leuconolide

intermediate would, however, be useful in the synthesis of leuconolide as well as the aglycone of carbomycin, and only minor modification (exchanging the 4-methoxy for a 4-methyl) would lead to the precursor for tylonolide. Degradation of leucomycin A_5 has given, after esterification, the methyl ester 61 in 70% yield[86] as well as 10% of 62 as described later in this chapter.



62

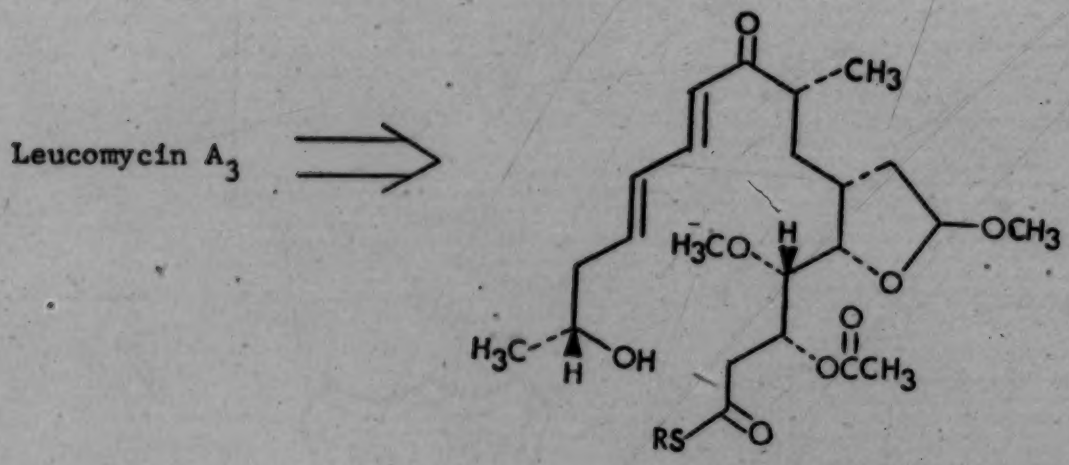
The overall synthetic approach to the aglycone of leucomycin is summarized in Figure 13.

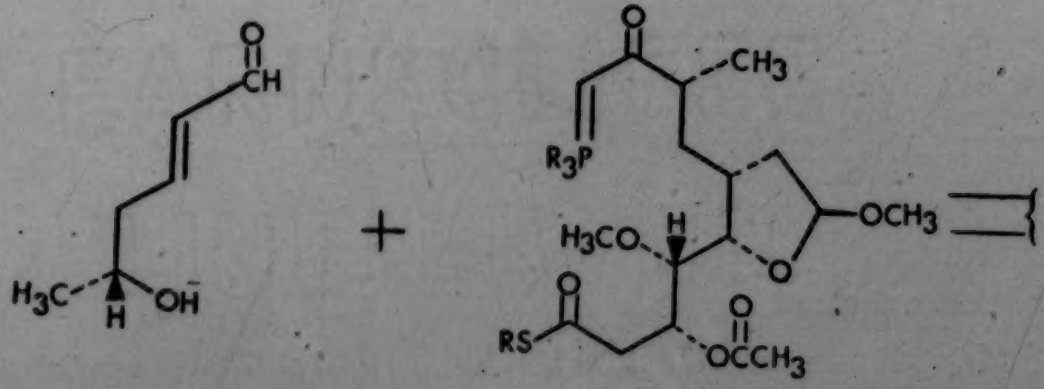
B) SYNTHESIS OF THE RACEMIC C_1-C_9 SEGMENT

The starting point enroute to the desired lactonic acid was the cis-diacid 10, also common to the methymycin synthesis. The first task involved improving the yield of this diacid.

In 1966, Cannell[90] reported the formation of bicyclo[4.2.1]nona-2,4,6-triene 4 during the pyrolysis

Figure 13: Synthetic Approach Towards Leuconolide

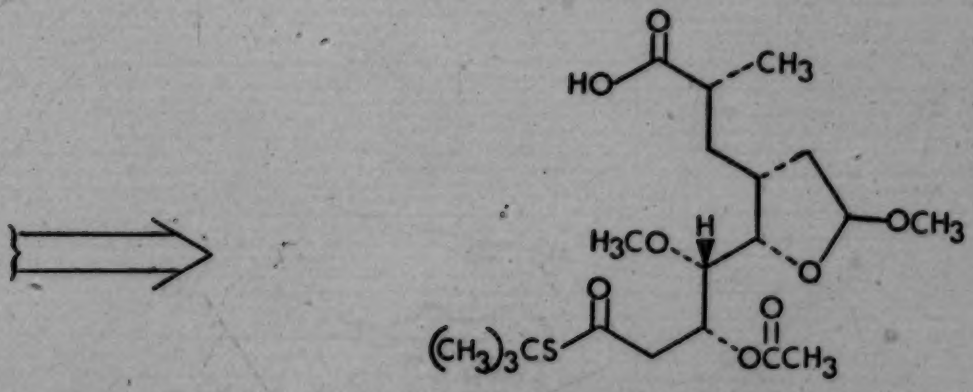




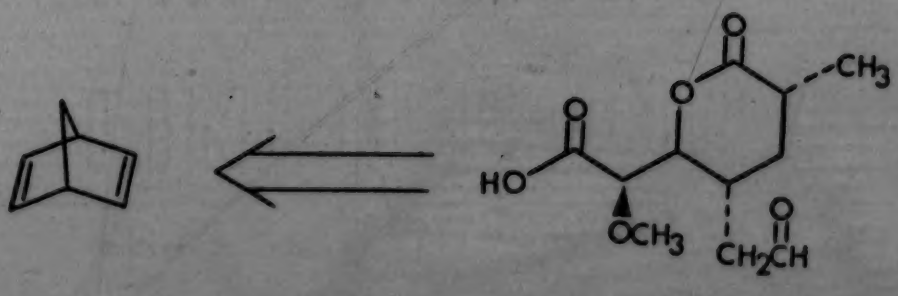
(R) Synthesized

Racemic

Figure 13 (Continued)

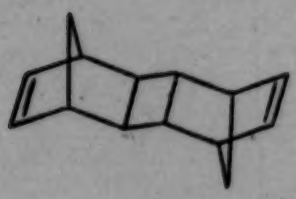


Synthesized

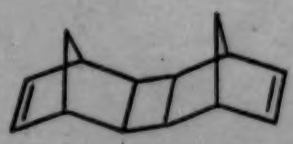


Or equivalent

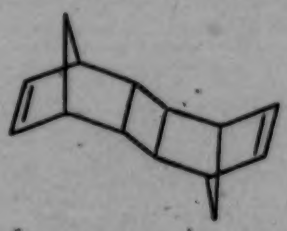
of the $[\pi_s^2 + \pi_s^2]$ dimers of norbornadiene. Schrauzer[87,88] reported that in the presence of bisfumaronitrile nickel(0), norbornadiene is dimerized to the anti-fused isomers 1, 2 and 3, the main product being 2 which accounts for approximately 80% of the mixture.



exo-anti-exo
1



endo-anti-exo
2



endo-anti-endo
3

The original procedure involved a sealed tube reaction. Application of this method to a large scale (350 g) resulted in a violent explosion. A better approach seemed to be use of nickel carbonyl in an open system.[89] The yields were good and the reaction was much safer to execute. The amount of isomer 2 in this mixture appeared to be almost identical to that obtained by the previous method.

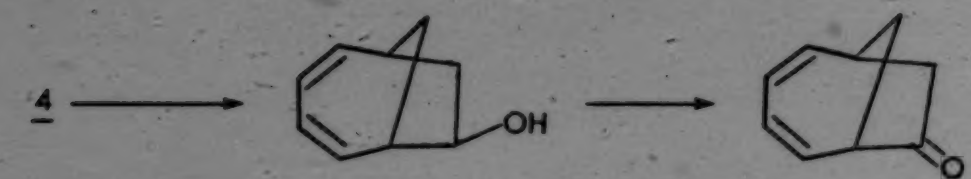
The dimeric mixture was pyrolized (300-360°) in a flow system to give 4 in 85% yield. Since the product distribution is a function of temperature, contact time and surface area, it was necessary to monitor the earlier fractions by ^{1}H-NMR spectroscopy to optimize conditions. Too high a temperature and/or too long a contact time produced an aromatic

4 5 6

material by further reaction of 4. This result is highly undesirable due to the extreme difficulty in separation of 4 from the aromatic by-product. Use of too low of a temperature resulted in incomplete cracking to exo-tricyclo[4.2.1 ^{2,5}]-nona-3,7-diene 6, a pyrolysis intermediate along with uncracked dimer. A typical experiment using a 2.5 x 35 cm column required an oven temperature of 350-360°, a flow of 40 ml per minute of carrier gas and a drop rate of 12 to 15 seconds.

The oxidation of the isolated double bond of 4 was accomplished in four steps. Hydroboration of 4 with bis(3-methyl-2-butyl)borane[91] proceeded in 75% yield without skeletal rearrangement to alcohol 7. The selectivity for the isolated double bond may be rationalized by assuming that conjugation in the diene portion results in reduced reactivity at that site.[105] From inspection of molecular models, the methylene bridge was found to be inclined slightly towards the plane of the diene, providing some shielding from exo

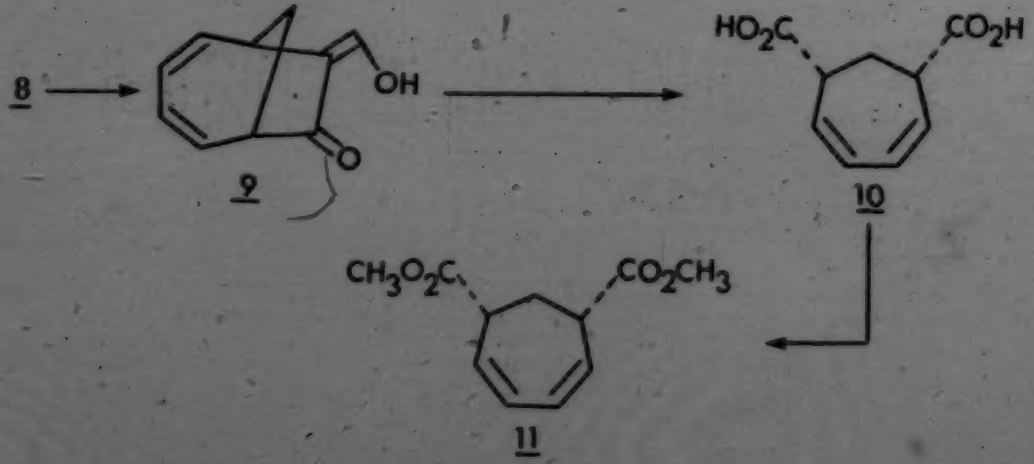
attack by the borane. The isomeric purity was ca. 90% and the hydroxyl group was shown to be in the exo-configuration using the lanthanide shift reagent $Eu(fod)_3$.[84]



7 8

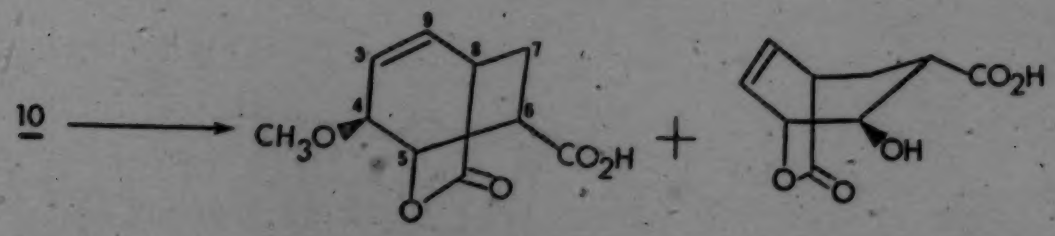
Activation of the C_8 position was accomplished by oxidation of the C_7 alcohol to the ketone 8. Oppenauer oxidation[92,93] using aluminum tert-butoxide[94] and 4-benzoquinone gave reasonable yields of 8. However, oxidation in dimethylsulfoxide using trifluoroacetic anhydride and triethylamine[95] proceeded in almost quantitative (94%) yield.

Acid functionality could now be introduced at the C_8 position by first preparing the hydroxymethylene derivative[96] 9, followed by subsequent oxidative cleavage with sodium meta periodate[97] to the diacid 10. These steps pro-



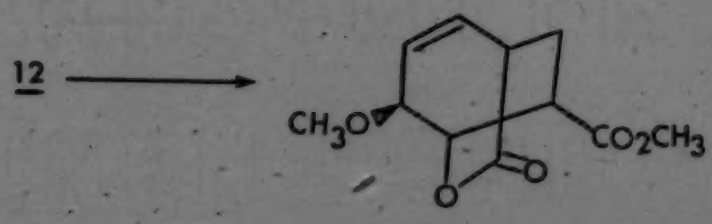
ceeded in good yield. The ^{1}H-NMR spectrum of the dimethyl ester 11 showed no evidence of the trans isomer.[98]

Epoxidation of the diacid 10 with m-chloroperbenzoic acid in methanol gave the desired acid 12 in about 50% yield after chromatography along with alcohol 13 in 35% yield.



12 13

The results of decoupling experiments for acid 12 are summarized in Table 4. Further confirmation of the structure of the acid was achieved by conversion of 12 to its methyl ester 14.



14

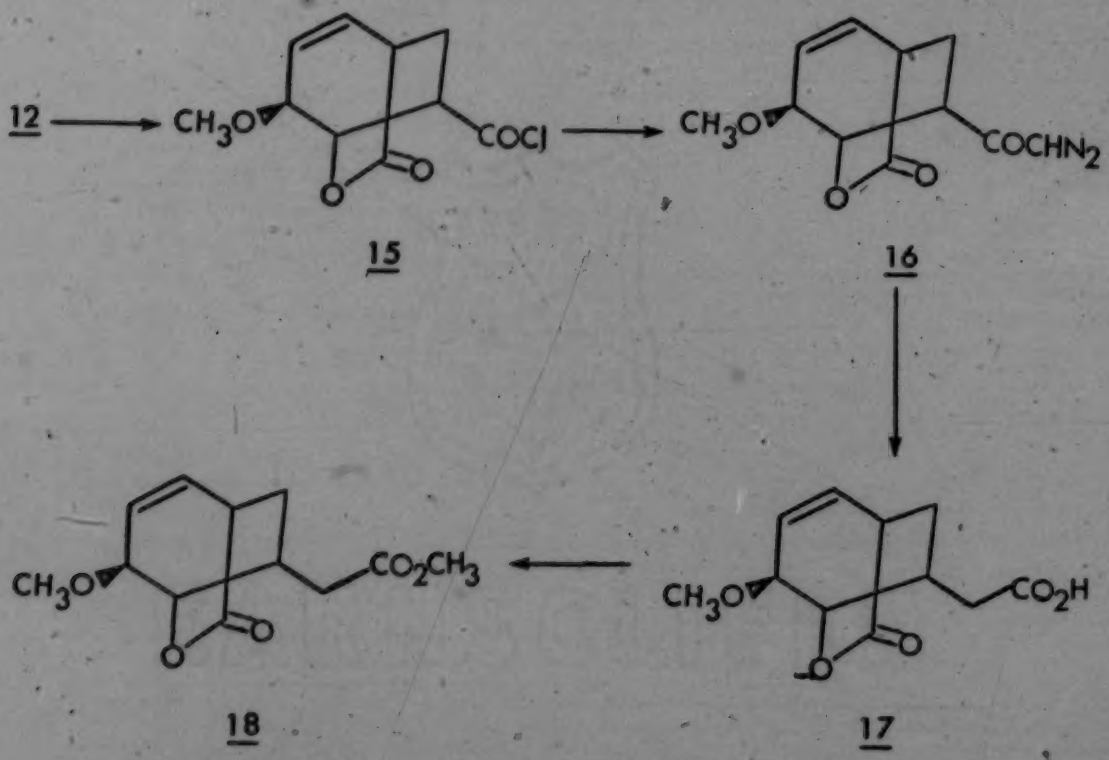
It was now necessary to prepare the homologous acid in order to ensure the correct number of carbons on the aldehyde side chain of the aglycone of leucomycin A_3. This was

Table 4: ^{1}H-NMR Decoupling Experiments for 12

Proton Irradiation (H)	Observed Change	J (Hz)
2.45(H_{7a},H_{7b})	H_8(2.3), d	H_8-H_9, 8.5
	H_6, *	
3.23(H_6,H_8)	H_7(2.35, 2.52), bd	
	H_5(5.16), dd	H_5-H_4, 4.0
		H_5-H_7, 1.8
	H_9(5.96), dd	H_9-H_3, 10.5
		H_9-H_4, 1.5
	H_3(5.76), bdd	H_3-H_9, 10.5
4.19(H_4)	H_5(5.16), bd	
	H_3(5.76), dd	H_3-H_9, 10.5
		H_3-H_8, 1.5
	H_9(5.96), dd	H_9-H_3, 10.5
		H_9-H_8, 8.5
5.17(H_5)	H_3(5.76), bdd	H_3-H_9, 10.5
	H_4(4.16), bd	H_4-H_9, 1.5
5.80(H_3,H_9)	H_4(4.16), d	H_4-H_5, 4.0
	H_5, *	
	H_8, *	
5.90(H_3,H_9)	H_4(4.16), bd	H_4-H_5, 4.0
	H_8(2.3), dd	H_8-H_{7a}, 2.5
		H_8-H_{7b}, 5.0

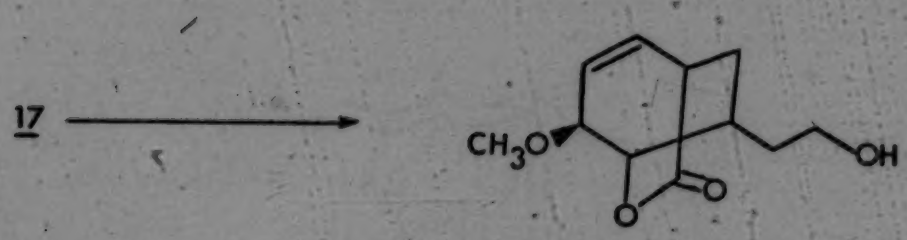
* Signal appears slightly altered

achieved by first converting the acid 12 to the corresponding acid chloride 15 with freshly distilled oxalyl chloride. If the starting acid was very pure, the corresponding acid chloride crystallized.

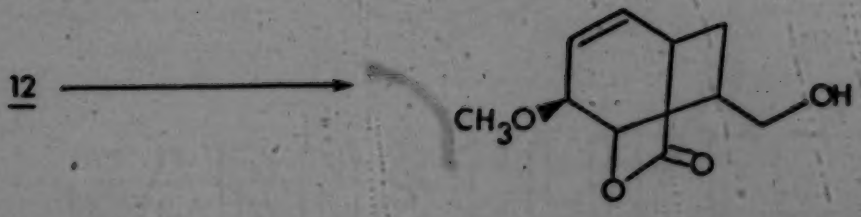


The acid chloride was treated with diazomethane to give diazocompound 16 as a yellow crystalline material after column chromatography on silica gel. The diazoketone was then photolyzed in wet tetrahydrofuran through a pyrex filter using a 450 W medium pressure Hanovia lamp to give acid 17 in 80% overall yield from 12. The chain extended acid was converted to its methyl ester 18 for further confirmation of the structure.

The acid 17 could now be reduced to alcohol 19 in 80% yield by first forming the mixed anhydride with ethyl chloroformate in the presence of triethylamine, followed by reduction with sodium borohydride. Subjecting acid 12 to the same conditions as 17 gave alcohol 101 in 40 to 50% yield.



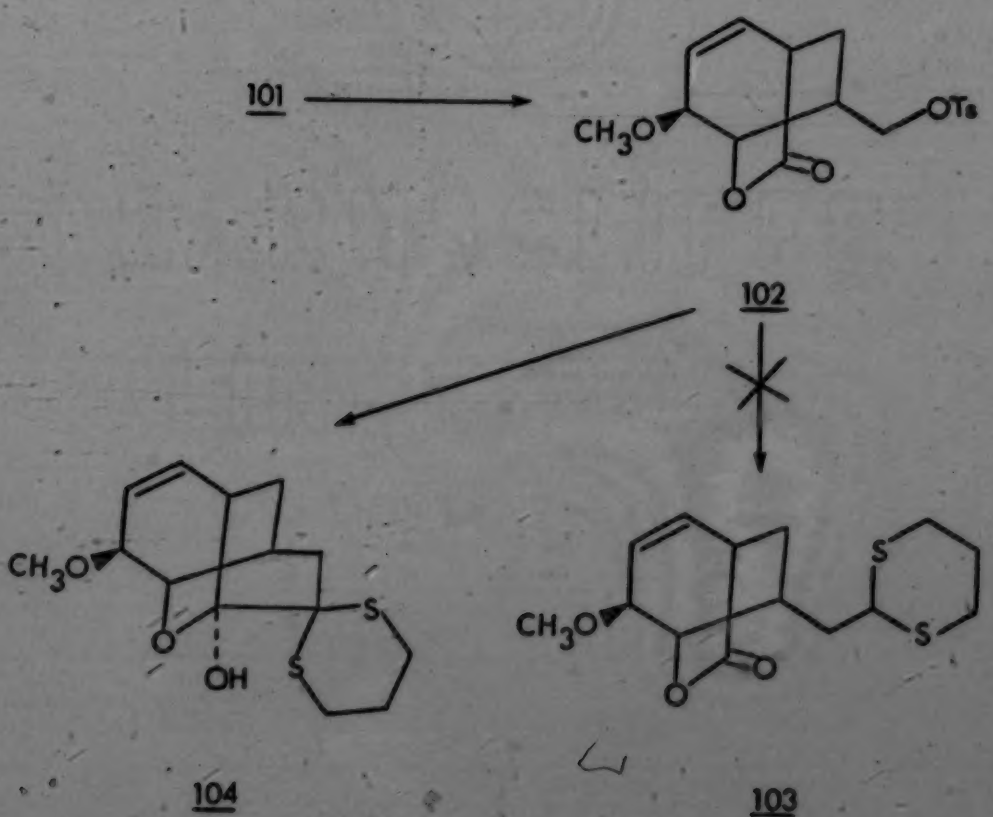
19



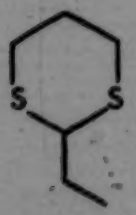
101

Since the primary alcohol carbon of compound 19 was to become the C-18 carbonyl carbon in the side chain of the target molecule, several methods for carbonyl formation and protection were investigated. It was hoped that a masked aldehyde could be generated by the following sequence of reactions. First, tosylation of alcohol 101 with tosyl chloride gave compound 102. Treatment of this compound with the

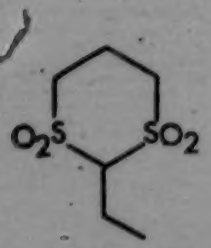
lithium anion of 1,3-dithiane[106] gave a single product. The product was not, however, the desired compound 103 as it exhibited no lactone carbonyl absorption in the infrared spectrum. It was postulated that this compound had the structure 104. Furthermore, since the Lemieux-von Rudloff oxidation is a necessary operation in a later step, model compound 2-ethyl-1,3-dithiane 105 was tested for its stability to these conditions. Unfortunately, tetraoxygenated compound 106 was the major product, as deduced from its mass spectrum. Thus the dithiane approach was abandoned.



104 103

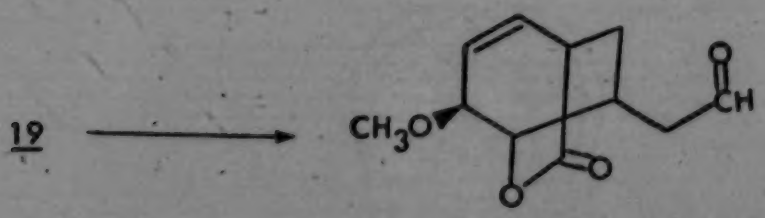


105



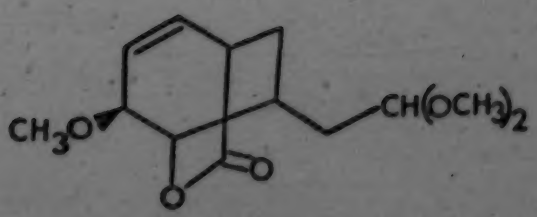
106

The suitability of protection as an acetal was next tested. The alcohol 19 was first oxidized to aldehyde 107, in 80% yield, with pyridinium chlorochromate, and subsequently converted to dimethyl acetal 108. Reduction of the dimethyl acetal at -15° with lithium aluminum hydride gave diol 109 and acetal 109a. Furthermore, diol 109 slowly changed to acetal 109a upon standing at room temperature. Treatment of the mixture with tosyl chloride, followed by

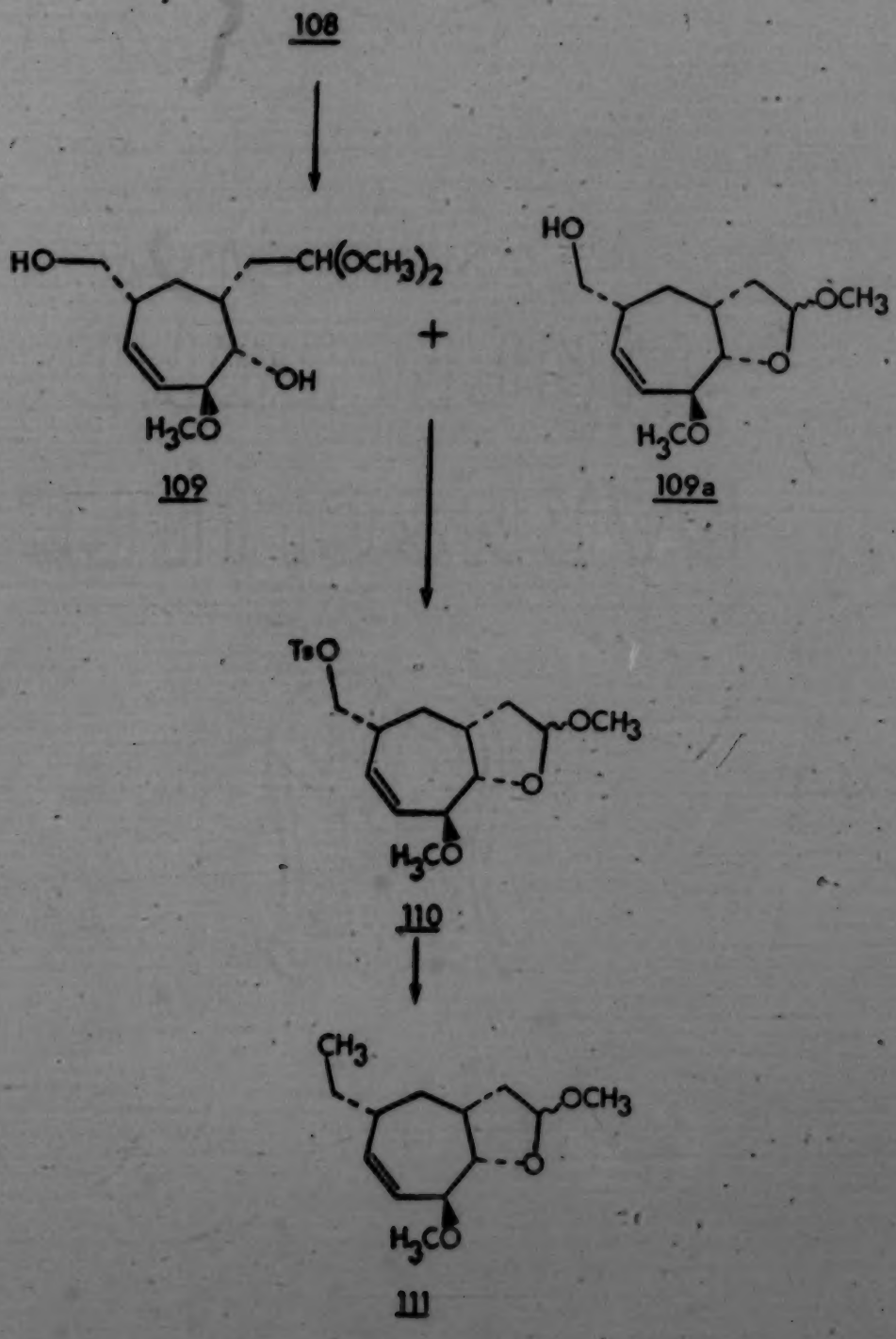


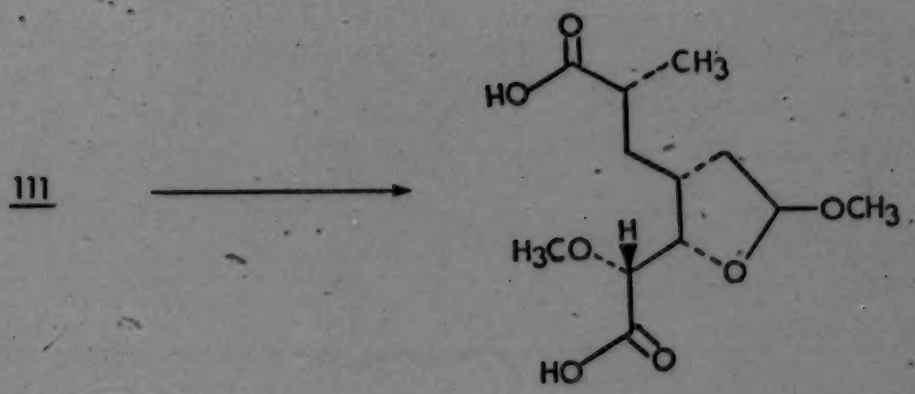
19

107



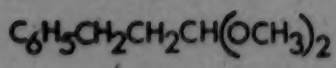
108


108
HO
CH(OCH3)2
OH
H3CO
109
+
HO
OCH3
O
H3CO
109a
TsO
OCH3
O
H3CO
110
CH3
OCH3
O
H3CO
111

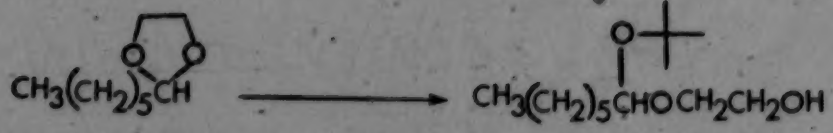


112

lithium aluminum hydride reduction, gave almost exclusively (ca. 80%) product 111. Lemieux-von Rudloff oxidation of this compound gave diacid 112 which was of no value since there was no easy way to distinguish between the two acid functionalities for future chemical operations. The dimethyl acetal approach was further rejected on the basis of the following model studies. In these studies, compound 113 was prepared by oxidation of 3-phenylpropanol with pyridinium chlorochromate, followed by protection as the dimethyl acetal. Subsequent oxidation, followed by VPC analysis, showed that dimethyl acetal 113 had decomposed. Also, preparation of the ethylene glycol acetal 114 by treatment of heptanaldehyde, followed by Lemieux-von Rudloff oxidation, gave exclusively one product, most likely 115 as determined from its ^{1}H-NMR spectrum.

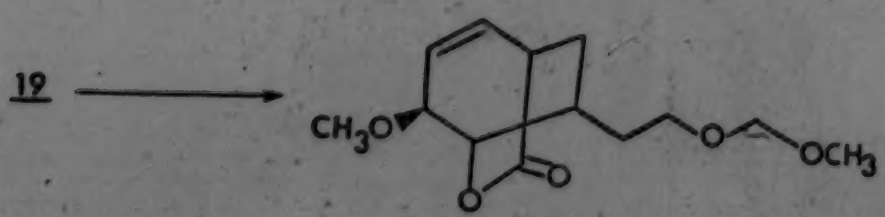


113



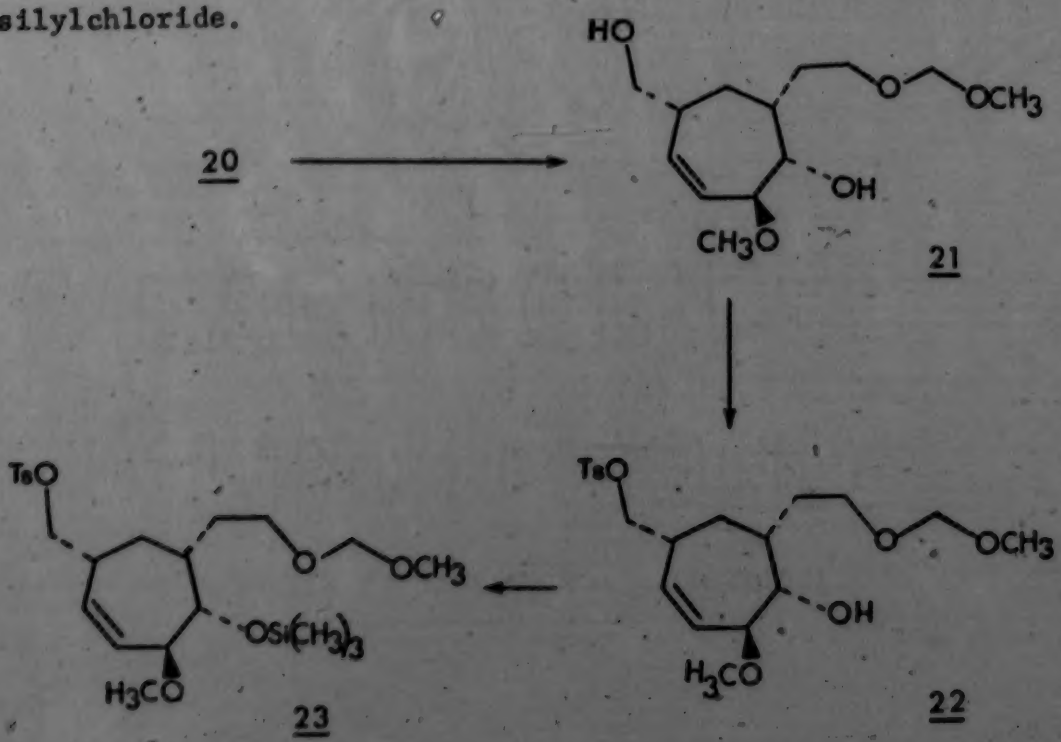
114 115

With these discouraging results, attention was focussed on the protection of the alcohol instead of the aldehyde. The methoxy methyl protecting group was selected and a more detailed discussion of this group is presented in Part II of this thesis. It was hoped that deprotection and oxidation to the aldehyde at a later stage might be feasible. Thus, treatment of alcohol 19 with chloromethyl methyl ether in the presence of a very hindered base such as diisopropylethylamine, gave ether 20 in quantitative yield.



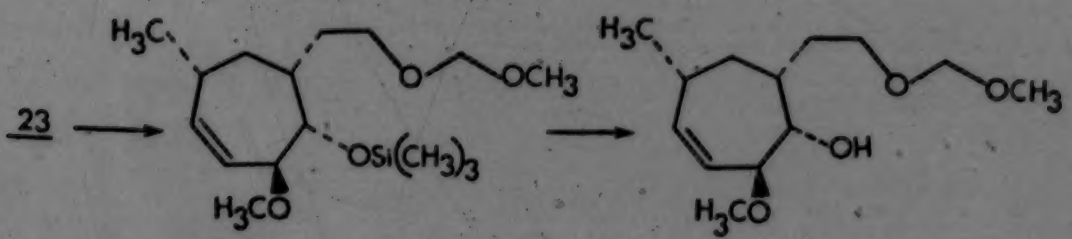
20

The lactone portion of 20 was reduced with lithium aluminum hydride to the resulting diol 21, again in quantitative yield and subsequent treatment of the diol with one equivalent of p-toluenesulfonyl chloride in pyridine gave tosyl compound 22. This functionality would lead to the desired methyl group in the C_3-C_9 segment. The maximum yield was 94%; however, in experiments where the yield was lower, extraction of the aqueous layer with chloroform gave recovered starting material. Protection of the secondary alcohol function of 21 was achieved by quantitative conversion to the tosyl silyl ether 23 with pyridine and trimethylsilylchloride.



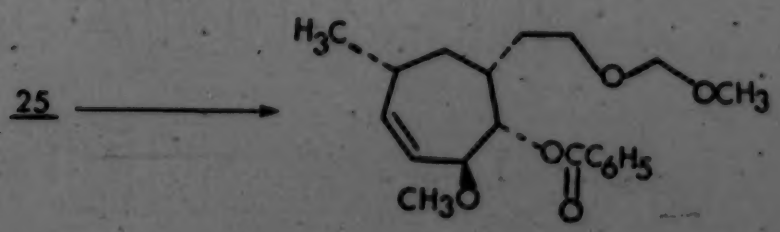
Reduction of 23 with lithium aluminum hydride proceeded as expected, to give silyl ether 24 in excellent (90%) yield.

Removal of the ether protection with a methanol solution containing a trace amount of trifluoroacetic acid gave alcohol 25 which could easily be purified by column chromatography over silica gel, resulting in a 96% yield of pure 25.



24 25

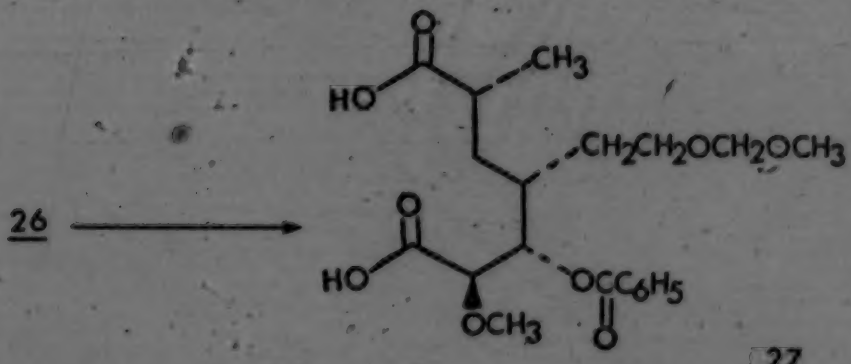
Compound 25 now meets all the requirements of a precursor of the desired lactonic acid. In order to facilitate isolation of the organic intermediate from the aqueous layer in the work-up stage of the Lemieux-von Rudloff oxidation, alcohol 25 was transformed to its benzoate 26.



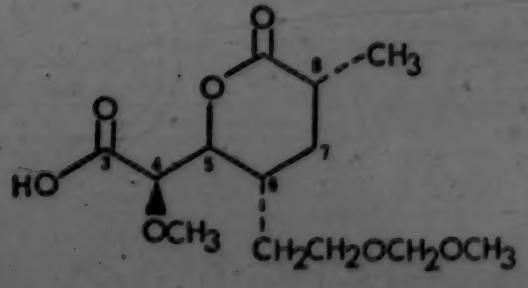
26

When 26 was treated with an aqueous tert-butyl alcohol solution of sodium meta periodate containing a catalytic amount of permanganate,[99] the double bond was oxidized

and benzoyloxy dicarboxylic acid 27 was obtained in 92% yield as a white, crystalline solid. The ^{1}H-NMR and infrared spectra were in accord with the proposed structure 27.



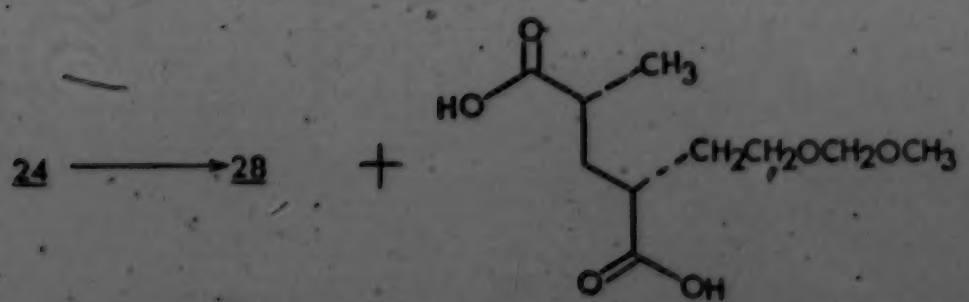
27



28

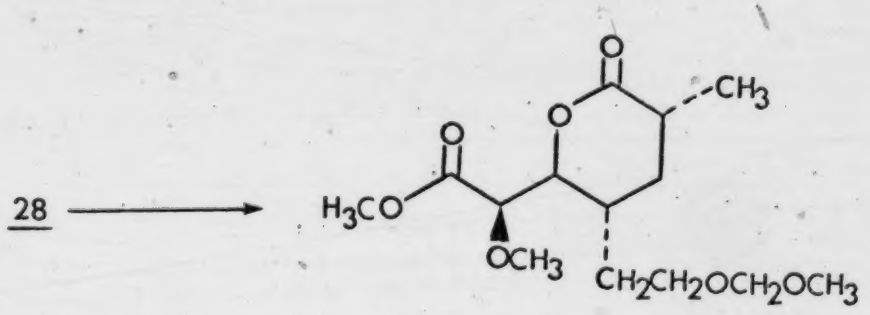
Treatment of 27 with aqueous 1.8 N potassium hydroxide solution, followed by acidification to pH=3, gave compound 28. However, epimerization apparently took place during the hydrolysis and the resulting product was contaminated with the C-4 epimer. This was deduced from the decrease in intensity and slight broadening of the methoxy signal at C-4. An attempt to hydrolyze the ester group with methanolic sodium methoxide also failed, starting material being recovered. Again, the signal at δ 3.5 was broadened.

Attention was now turned to silyl ether 24 which could be obtained from alcohol 25 in hope that oxidation, followed by acidification, would give the desired lactonic acid directly. Indeed when silyl ether 24 was subjected to the oxidation reaction, and acidified to pH-3, using bromocresol green indicator, lactonic acid 28 was obtained free from its C-4 epimer. The yield of the white crystalline compound was approximately 50% after purification by column chromatography, followed by recrystallization from an ether-pentane mixture. Also isolated was a slower moving fraction containing a compound thought to be 116. It was noted that if the pH was allowed to become lower than ca. 2.5, almost no lactonic acid could be isolated and diacid 116 was the major product. The structure of 28 was



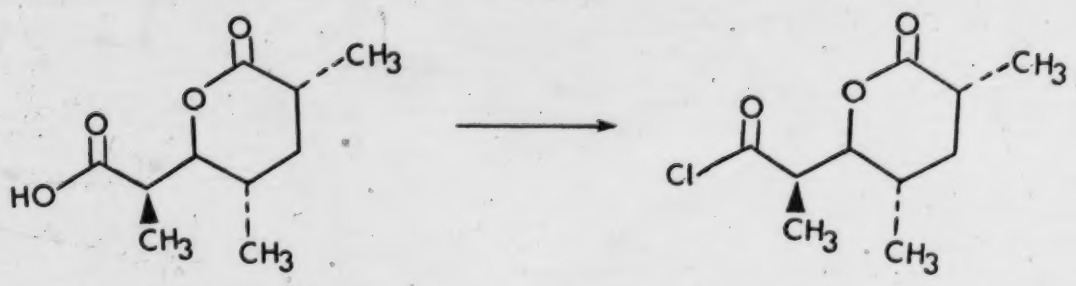
116

confirmed by ^{1}H-NMR, mass spectrum and elemental analysis. Furthermore, irradiation of the double doublet of δ 4.58 (H-5) caused the doublet at δ 3.96 (H-4) to collapse to a singlet. Treatment of lactonic acid 28 with ethereal diazomethane gave methyl ester 29. Similarly, irradiation of the signal at δ 4.49 of 29 caused the collapse of the doublet at δ 3.93 to a singlet.

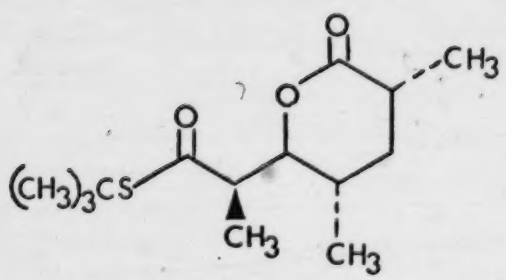


29

In this way, we have obtained the key intermediate analogous to the Djerassi-Prelog lactonic acid, necessary for the synthesis of the right-hand side of leuconolide A_3 as well as the aglycone of carbomycin. It would seem that one possible general route applicable to the synthesis of several macrolide antibiotics is through this type of lactonic acid intermediate. For instance, during the synthesis of methymycin, the P-D lactonic acid 117 was converted to the acid chloride 118 with oxalyl chloride and further reacted with 2-methylpropane-2-thiol to give 119 prior to ring opening.

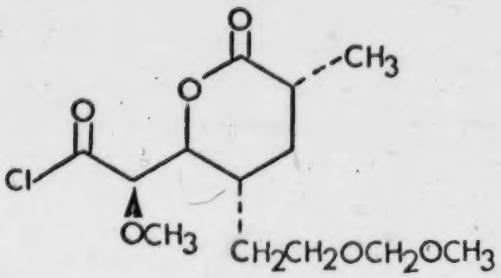


117 118

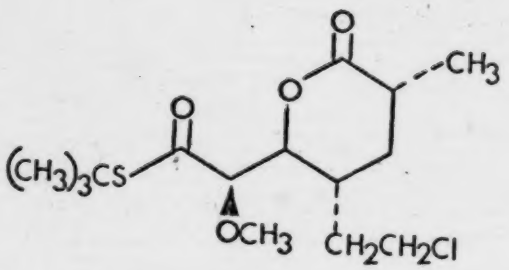


119

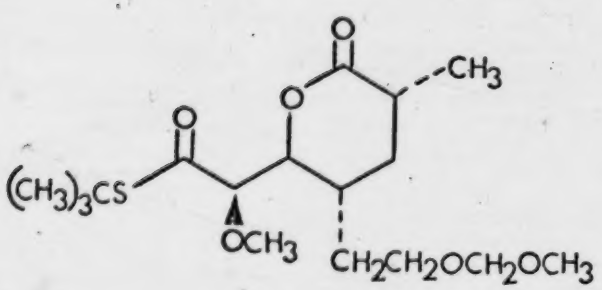
This approach was adopted for the present synthesis, however, when lactonic acid 28 was treated with excess oxalyl chloride in benzene, followed by addition of 2-methyl-propane-2-thiol, the desired thiol ester 30 was not obtained.



120



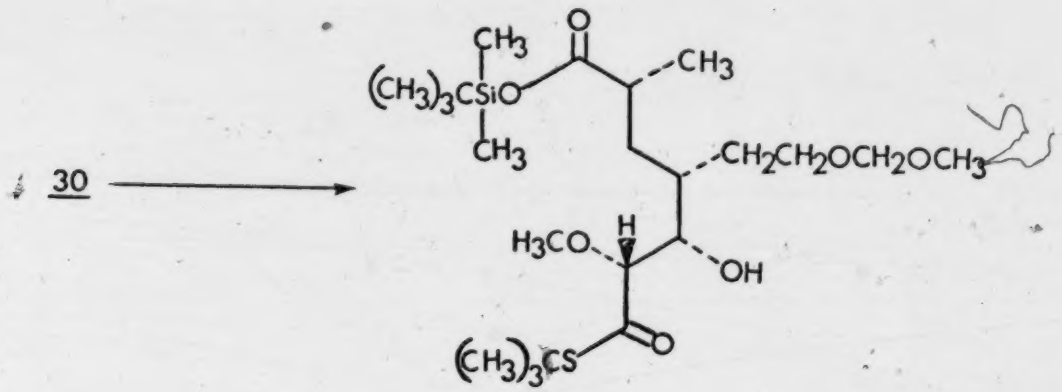
30a



30

Instead, the recovered product had a molecular weight of 336.5 and the ^{1}H-NMR signals for the methoxy methyl signals were absent. These facts led to the proposed structure 30a. However, this structure was not fully confirmed. A milder method was obviously necessary to prepare this thiol ester. An elegant procedure was reported by Masamune and co-workers.[100] The lactonic acid 28 was converted via the carboxylic phosphoric anhydride (formed by reaction with diethylphosphorochloridate and triethylamine) to the thiol ester 30 with thallium (I) 2-methylpropane-2-thiolate in 50% yield after purification by column chromatography. Unfortunately,

compound 30 was shown to be stable to ring opening. Treatment of 30 in tert-butyl alcohol with a dilute aqueous potassium solution, for 10 hours at 60°, followed by trapping of the dry (in vacuo) potassium salt with tert-butyldimethylsilylchloride, gave 121 in low (20%) yield, along with recovered starting material (50%). It is, therefore, necessary to make further improvements in this conversion.

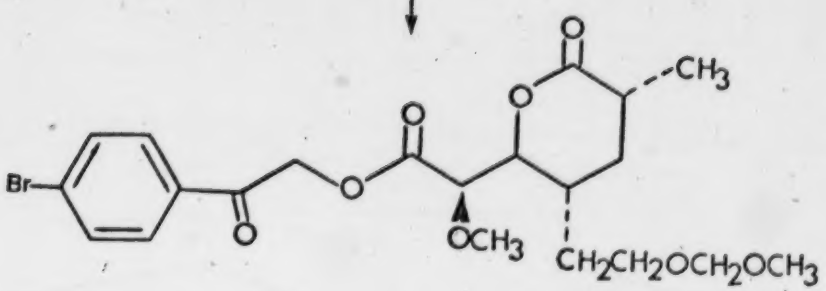


121

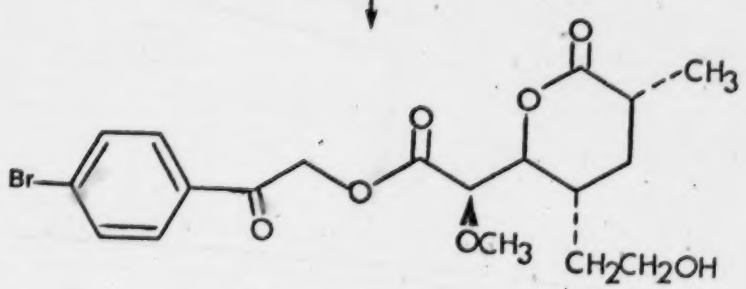
Rather than attempting to modify the conditions of the conversion, attention was turned to another possible route. This involved the conversion of the deprotected primary alcohol 54 to the aldehyde, followed by ring opening of the 6-membered lactone and cyclization to a 5-membered hemiacetal. In order to cleave the methoxy methyl blocking group, it was necessary to protect the acid. Direct treatment of lactonic acid 28 with trimethylsilylbromide did

effect deprotection, however, the product was difficult to isolate and tended to decompose under the reaction conditions. Protection of the acid, as its methyl ester, seemed to be impractical due to the harsh conditions necessary to hydrolyze the ester at a later stage. Instead, the phenacyl ester was prepared according to the procedure reported by Hendrikson.[103] This ester group is easily removed under mild conditions by treatment with zinc in acetic acid. Reaction of lactonic acid 28 with p-bromophenacyl bromide gave p-bromophenacyl ester 31 in 95% yield. Cleavage of the methoxy methyl group was accomplished by reaction with trimethylbromosilane in carbon tetrachloride, followed by quenching with methanol. The resulting alcohol 32 was obtained in 86% yield. Oxidation of 32 with pyridinium chlorochromate, as reported by Corey,[104] gave aldehyde 33 in 90% yield. Just prior to cleavage of the p-bromophenacyl ester, it was thought to be advantageous to protect the aldehyde as the dimethyl acetal. However, treatment of aldehyde 33 with methyl orthoformate containing a catalytic amount of trifluoroacetic acid did not give the desired acetal, but instead gave products 34 and 35. The ^{1}H-NMR spectra of methyl esters 34 and 35 were similar to that of esters 36 and 37 from natural leuconolide. This acid-catalyzed lactone ring opening, followed by lactol ether formation, was an interesting result and will be referred to again later in this chapter.

28


Br
O
O
O
O
O
CH3
OCH3
CH2CH2OCH2OCH3

31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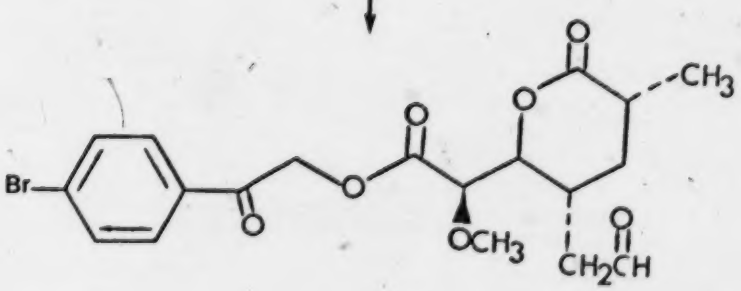
O
O
O
O
CH3
OCH3
CH2CH2OH

32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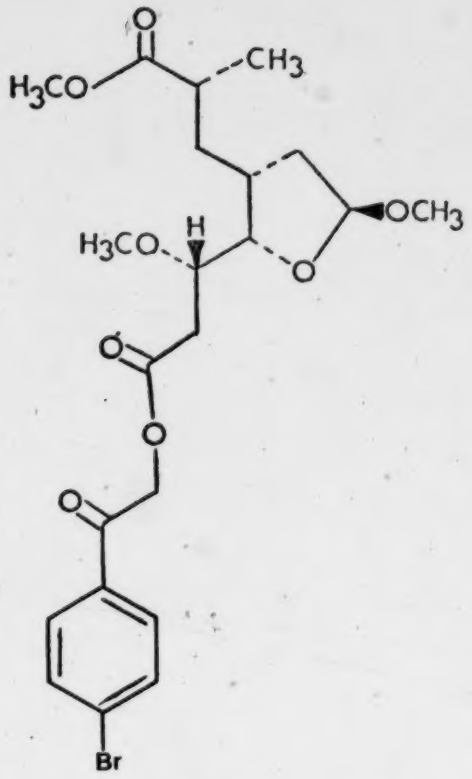
O
O
O
O
CH3
OCH3
CH2CH
O

33



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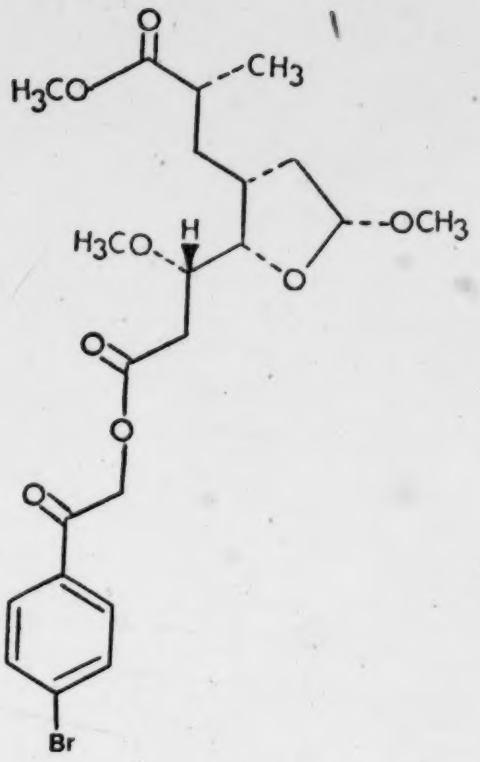

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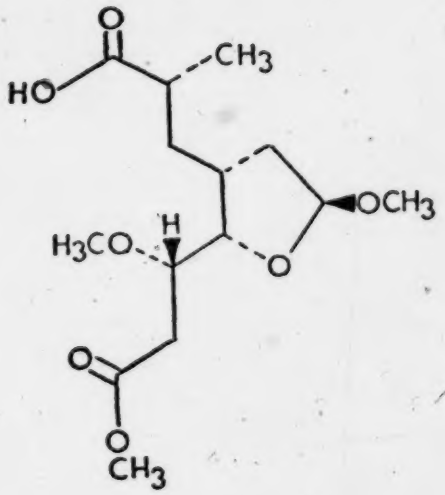

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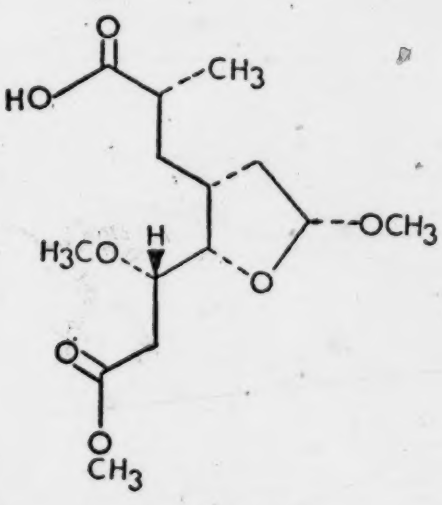
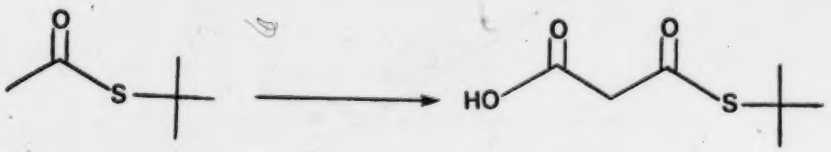


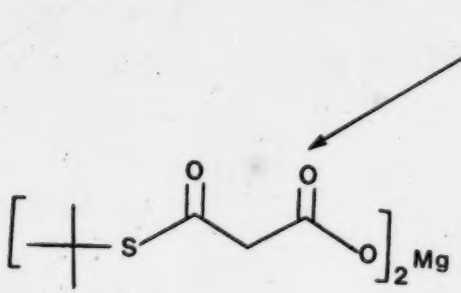
37

In order to overcome the problems encountered in protecting the acid functionality, it was decided to proceed directly with the chain extension prior to ring opening.

Recently, a mild and efficient C-alkylation via the Mg salt 40 was reported[129] which had the added advantage that it proceeded under virtually neutral conditions. The magnesium salt 40 was prepared by reaction of tert-butylthiolate 38 with lithium diisopropylamine, followed by addition of carbon dioxide. Subsequent acidification gave malonic acid thiol half ester 39 which, upon reaction with magnesium ethoxide, gave the white solid magnesium reagent 40.



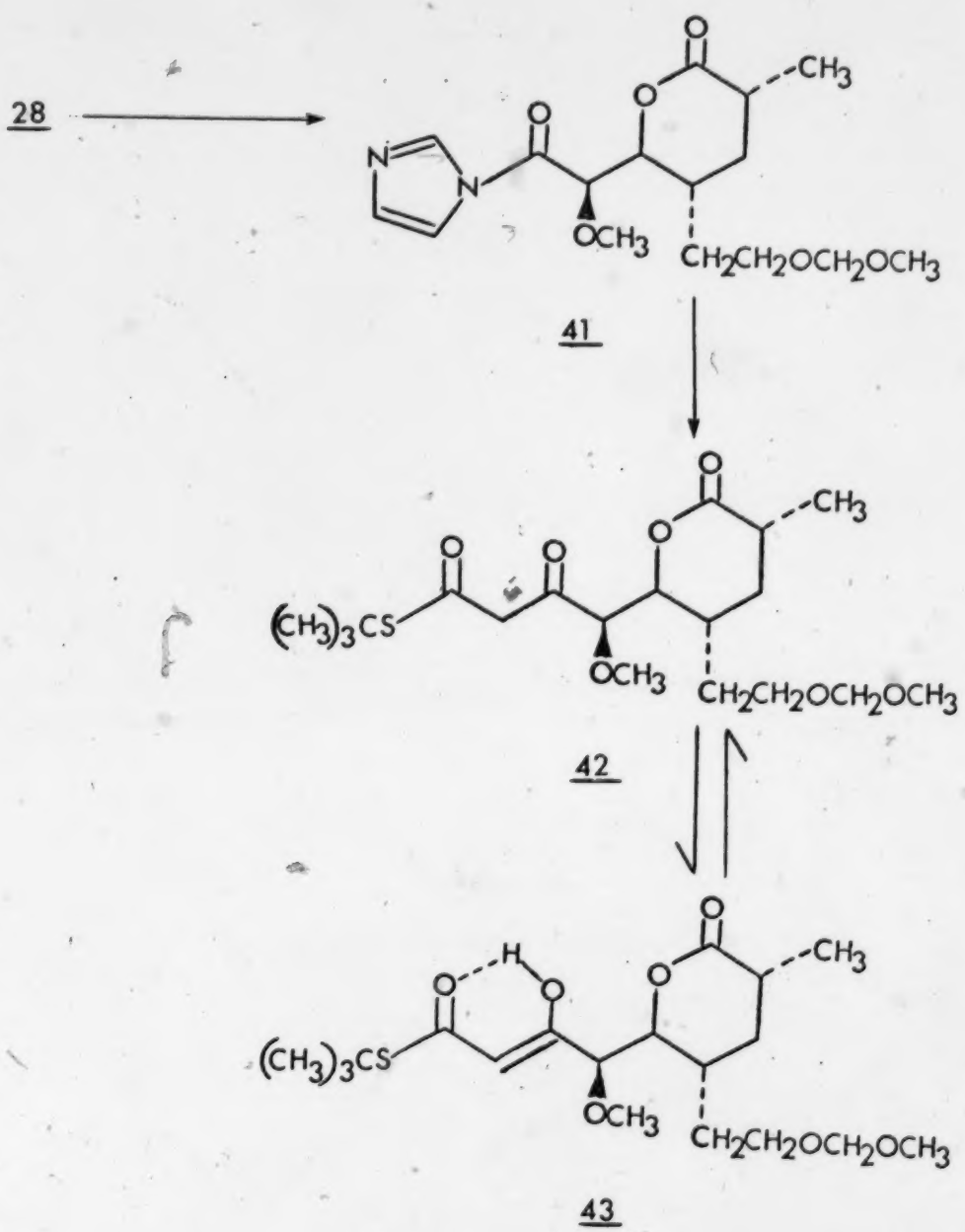
38 39



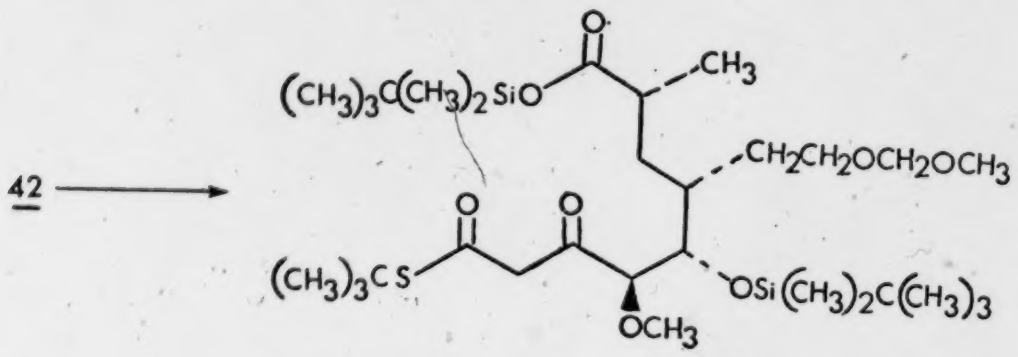
40

The lactonic acid 28 was activated for condensation with 40 by conversion to the acid imidazolide 41 with carbonyldiimidazole. The imidazolide was not isolated, but was dir-

ectly treated with the neutral magnesium salt 40 to give β-ketothiol ester 42 in excellent (94%) yield as a white solid. This solid keto form slowly equilibrated with its enol form 43 when left in the NMR tube in $CDCl_3$ over night.

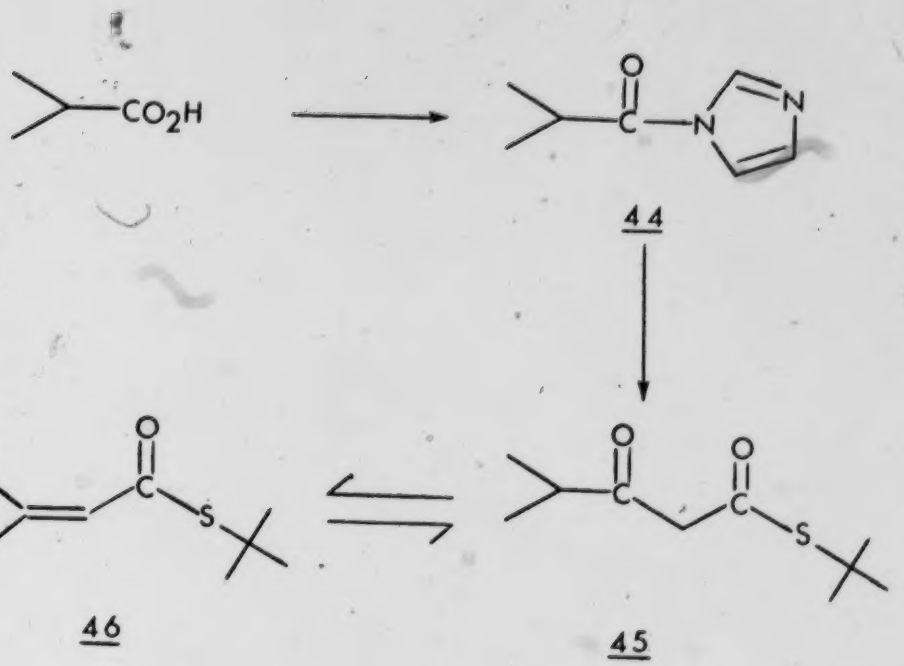


The ratio of 42:43 was approximately 3:1, as estimated by ^{1}H-NMR spectroscopy. This very important intermediate 42 contains the necessary C_1-C_9 carbons for the desired right hand side. Attempted lactone ring opening with potassium hydroxide and trapping, using imidazole and tert-butyldimethylsilyl chloride in dimethylformamide, did not yield the desired compound 42a.[106] This was a particularly discouraging result since it is necessary to liberate the C-9 carbon as an acid for further extension at this site.



42a

Attention was next focussed on the removal of the methoxy methyl protection. Before any further reactions were carried out, it was necessary to prepare and test a suitable model compound. Therefore, reaction of isobutyric acid with carbonyldiimidazole gave the corresponding imidazolide which, upon reaction with magnesium salt 40, gave β-ketothiol ester 45 in equilibrium with its enol form 46.[101]

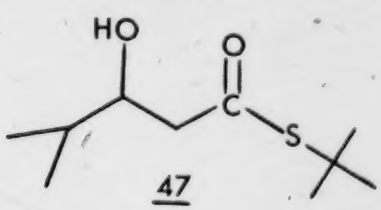


44

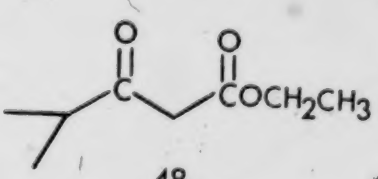
46

45

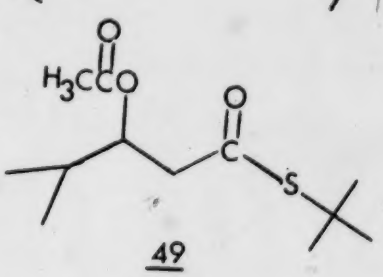
Attempts to reduce the keto function by hydrogenation (5% Pt-C) in ethanol did not give the desired alcohol 47, but rather the ethyl ester 48 (20%) along with recovered starting material. Compound 47 could, however, be obtained in quantitative yield from reduction of 45 with methanolic sodium borohydride at -20°C. The desired model compound 49 was finally available by reaction with acetic anhydride in pyridine in 70% yield.



47

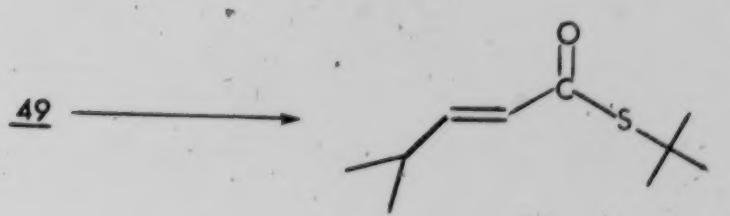


48



49

There follows a summary of the model studies which were reformed on the β-ketothiol ester system. Treatment of β-acetoxythiol ester 49 in tert-butyl alcohol with aqueous 0.2 N potassium hydroxide at 0° for three hours gave exclusive elimination[106] to 50. It was also found that treatment of 49 with imidazole in dimethylformamide gave 50% elimination to 50 along with dimerization after 24 hours at 60°.

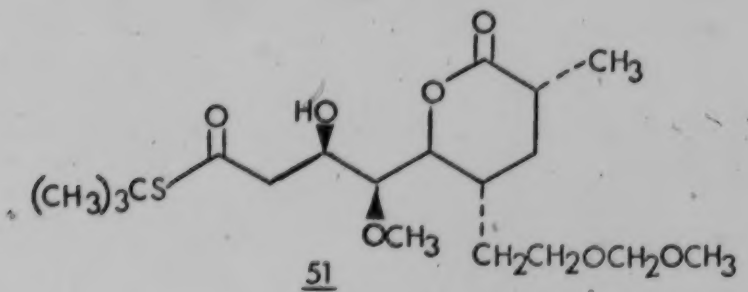


50

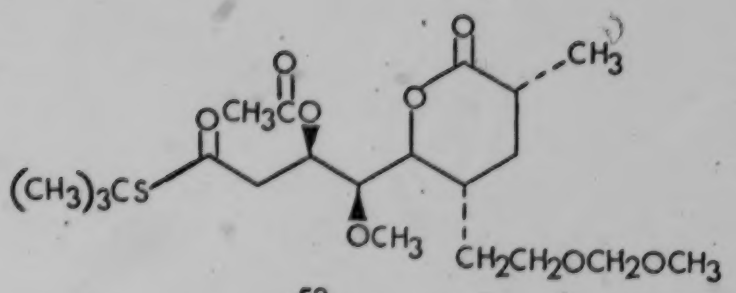
Fortunately, however, compound 49 survived when treated with a 1:1 mixture of acetonitrile and water containing 1% trifluoroacetic acid as well as under oxidation conditions with pyridinium chlorochromate when buffered with sodium acetate. When treated with 1.2 equivalents of trimethylbromosilane, compound 49 was recovered (90%) virtually unharmed.

These two results were encouraging and attention now returned to the macrolide system. The β-ketothiol ester 42 was reduced by Professor Yamamoto of this laboratory and compound 51 was obtained in 60% overall yield. The details of this procedure appear in his research report.[106] Subse-

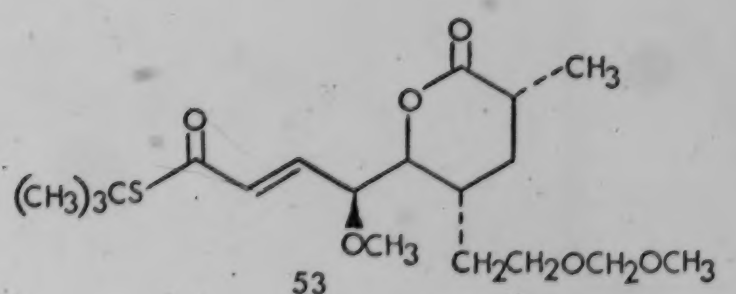
quent treatment of alcohol 51 with a 2:1 mixture of pyridine and acetic anhydride gave the β-acetoxythiol ester 52 in 65% yield, along with elimination product 53 in 33% yield after separation. The decoupling experiments on compound 52 are summarized in Table 5.



51



52



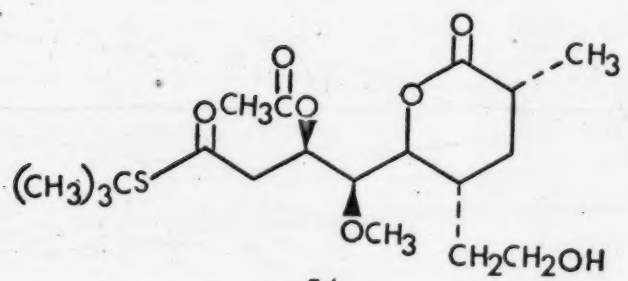
53

Table 5: ^{1}H-NMR Decoupling Experiments for 52

Proton Irradiation (H)	Observed Change	J (Hz)
2.24(H_6)	H_5, d	J_d=1.0
	H_{7a}, bt	J_t=12.0
	H_{7e}, dd	J_d=12.0, J_d=4.0
	H_{17a}, dbt	J_d=14.0, J_t=5.5
	H_{17e}, ddd	J_d=14.0, J_d=7.0 J_d=6.0
2.5(H_8)	Me-8, s	
	H_{7a}, bt	J_t=12.5
	H_{7e}, dd	J_d=12.5, J_d=4.0
3.60(H_{18e},H_4)	H_3, dd	J_d=7.3, J_d=3.8
	H_5, d	J_d=9.2
	H_{17a}, dd	J_d=14.0, J_d=8.7
	H_{17e}, dd	J_d=14.0, J_d=4.0

Successful cleavage of the methoxy methyl protecting group of 52 was accomplished by use of trimethylsilyl bromide to give alcohol 54 in 62% yield. The decoupling experiments for 54 are summarized in Table 6.

52



54

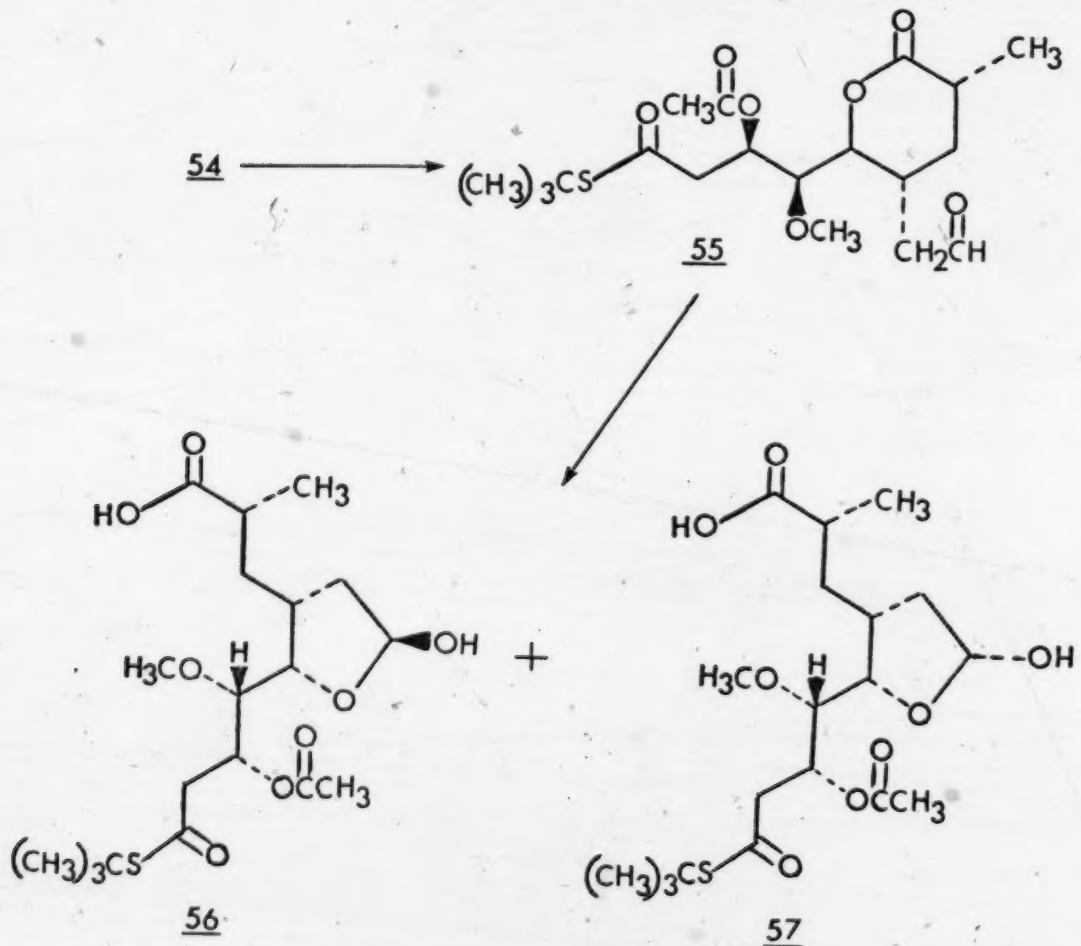
Table 6: ^{1}H-NMR Decoupling Experiments for 54

Proton Irradiation (H)	Observed Change	J (Hz)
2.26(H_6)	H_5, d	J_d=1.3
	H_{7a}, H_{7e}, *	
3.65(H_4)	H_3, d	J_d=9.0
4.32(H_5)	H_4, d	J_d=6.3
	H_6, *	
	**	
5.50(H_3)	H_4, d	J_d=1.3
	H_{2a}, d	J_d=16.0
	H_{2e}, d	J_d=16.0
C-3 epimer		
5.40(H_3)	H_{2e}, d	J_d=16.0
	H_{2a}, d	J_d=16.0

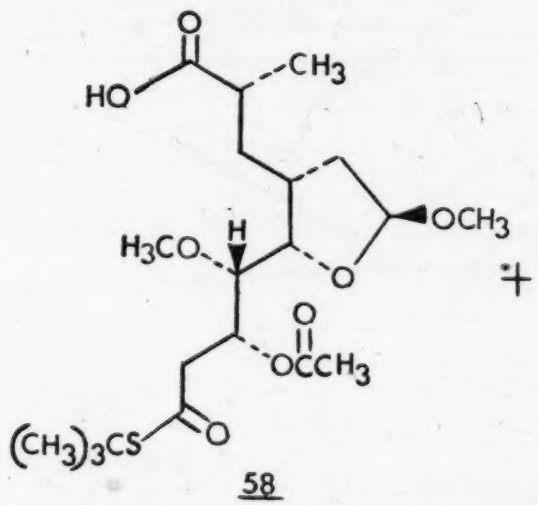
* Some change observed

** H_3 proton was not recorded on the spectrum

The alcohol 54 was then oxidized with pyridinium dichromate[108] to the corresponding aldehyde 55 in 65% yield after purification. This aldehyde was unstable at room temperature for long periods of time and slowly re-arranged to the hemiacetal mixture 56 and 57. Treatment of aldehyde 55 with a 1:1 mixture of acetonitrile and water containing 1.5% trifluoroacetic acid for 1.5 hours, gave crude hemiacetal mixture 56 and 57 in 70% yield. The crude hemiacetal mixture was directly treated with methyl orthoformate and trifluoroacetic acid in methanol to give 60% of 58 and 59.

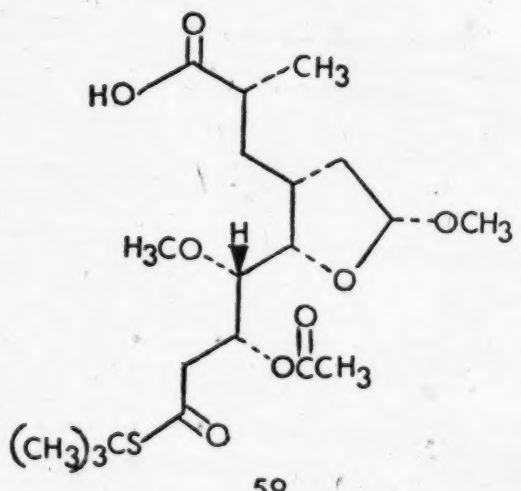


56 + 57



58

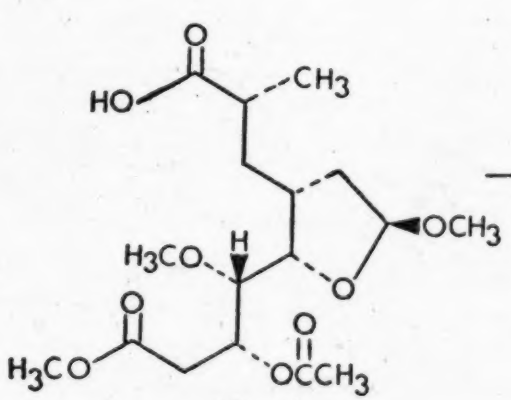
+



59

The series of reactions 51 to 58 and 59 have been examined only in preliminary form and the yields have not been optimized.

Up to this point, there was no strong evidence that the asymetric carbons had the correct configuration. That the stereochemistry is indeed correct is based on the fact that compounds 58 and 59 closely resembled compound 60 in pattern and coupling when compared by ^{1}H-NMR spectroscopy. The source of 60 was degradation of natural leuconolide A_5.[86]



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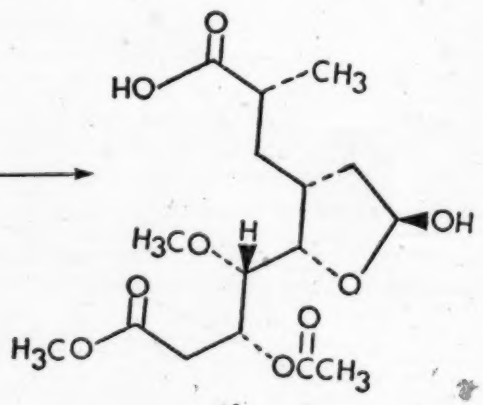
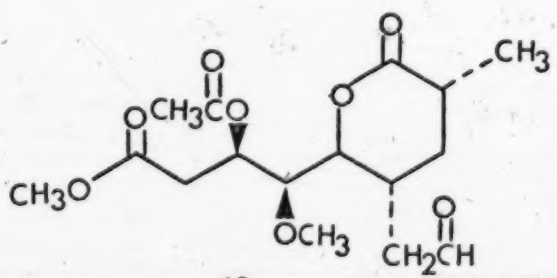


61

+



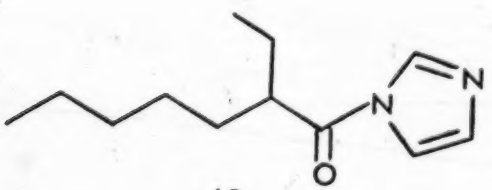
62

Leucomycin A_5

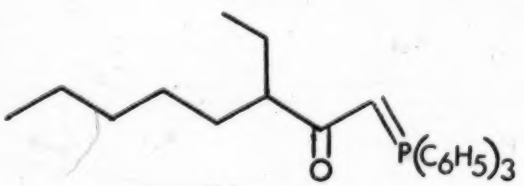
Another interesting point emerged from the degradation studies. When 60 was treated with difluoroacetic acid or acetic acid,[106] compound 61 was obtained in 70% yield, along with aldehyde 62 in 10% yield. The ^{1}H-NMR spectrum of 55 (obtained earlier) closely resembled that of aldehyde 62. The chemical shifts for 62 are shown in Table 7.

With the successful isolation of 58 and 59, the synthesis of the C_1-C_9 unit was complete. The centers appeared to have the correct stereochemistry.

Model studies were next carried out to determine the feasibility of preparing a phosphorane from 60. Imidazolide 63 was prepared by reaction of 2-ethylhexanoic acid and carbonyldiimidazole in quantitative yield. Treatment of 63 with salt free triphenylmethylene phosphorane[110] gave phosphorane 64[111] in 90% yield.



63



64

This procedure was applied to 60 (from natural leuconolide). Therefore, 60 was converted to 65 and then to 66. It appears

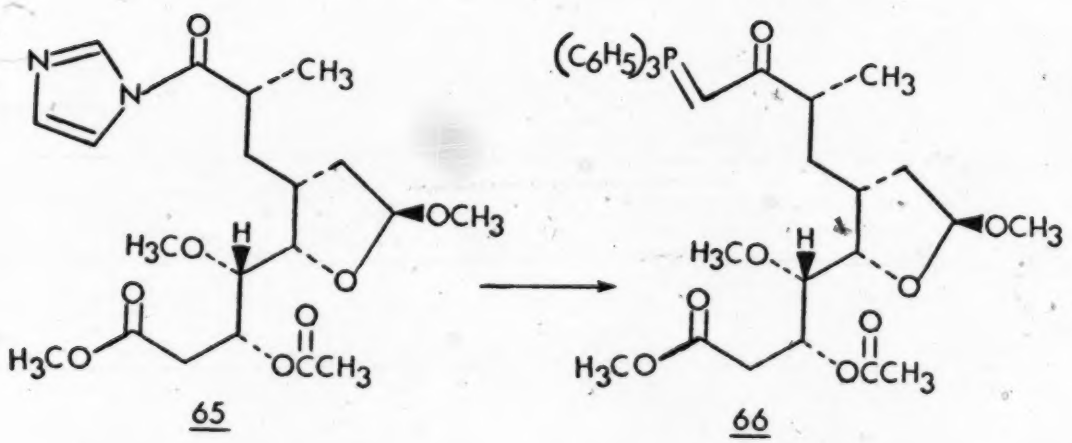
Table 7: Chemical Shifts for 62*

^{1}H-NMR ($CDCl_3$): 1.24 (d, J_d=7.0, 3H), 2.08 (s, 3H), 2.6 (m, 6H), 2.80 (dd, J_d=16.0, J_d= 6.5, 1H), 2.86 (dd, J_d=16.0, J_d=4.5, 1H), 3.53 (s, 3H), 3.65 (dd, J_d=5.0, J_d=1.5, 1H), 3.70 (s, 3H), 4.30 (dd, J_d=10, J_d=1.5, 1H), 5.55 (m, 1H), 9.80 (bs, 1H).

* J (Hz)

that if this route could be successfully applied to thiol esters 58 and 59, subsequent coupling with the left-hand side would very likely be possible. Unfortunately, there was not enough of these two esters available at this time to test this route.

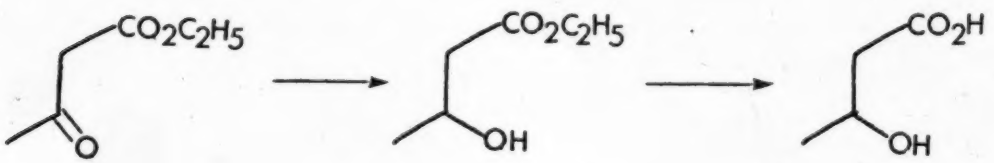
60



65 66

C) SYNTHESIS OF THE OPTICALLY PURE C_{11}-C_{15} SEGMENT

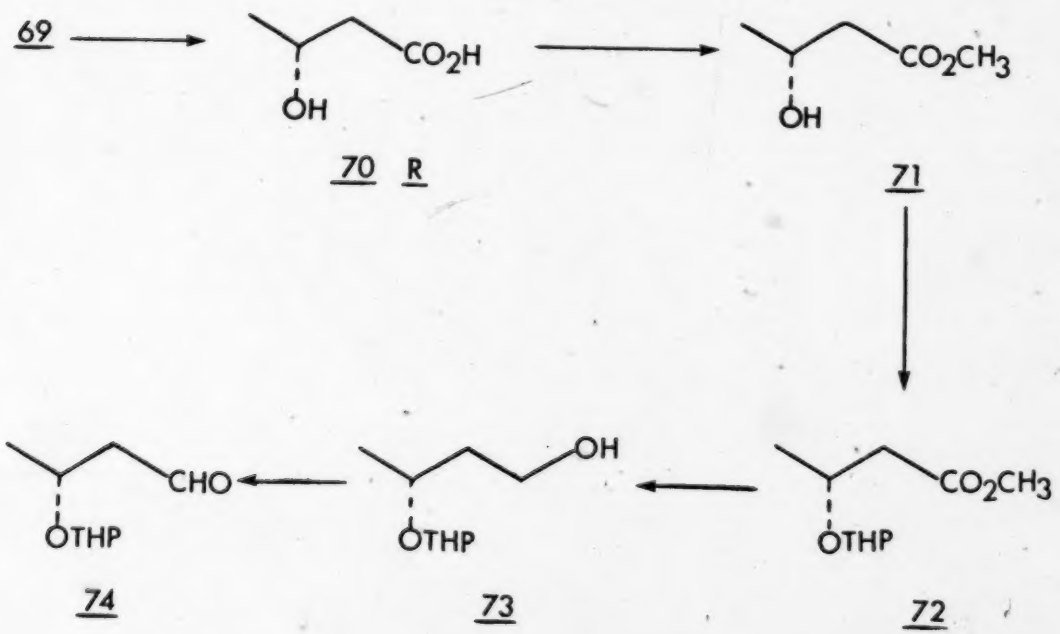
In this section, the synthesis of the optically active left-hand segment is discussed. Although β-hydroxybutyric acid is commercially available, it was found to be insufficiently pure for our purposes, therefore, the following procedure was adopted. Ethyl acetoacetate 67 was reduced with methanolic sodium borohydride to compound 68 in 65% yield. Saponification of hydroxyester 68 with aqueous 4 N sodium hydroxide gave β-hydroxybutyric acid 69 in 75% yield.

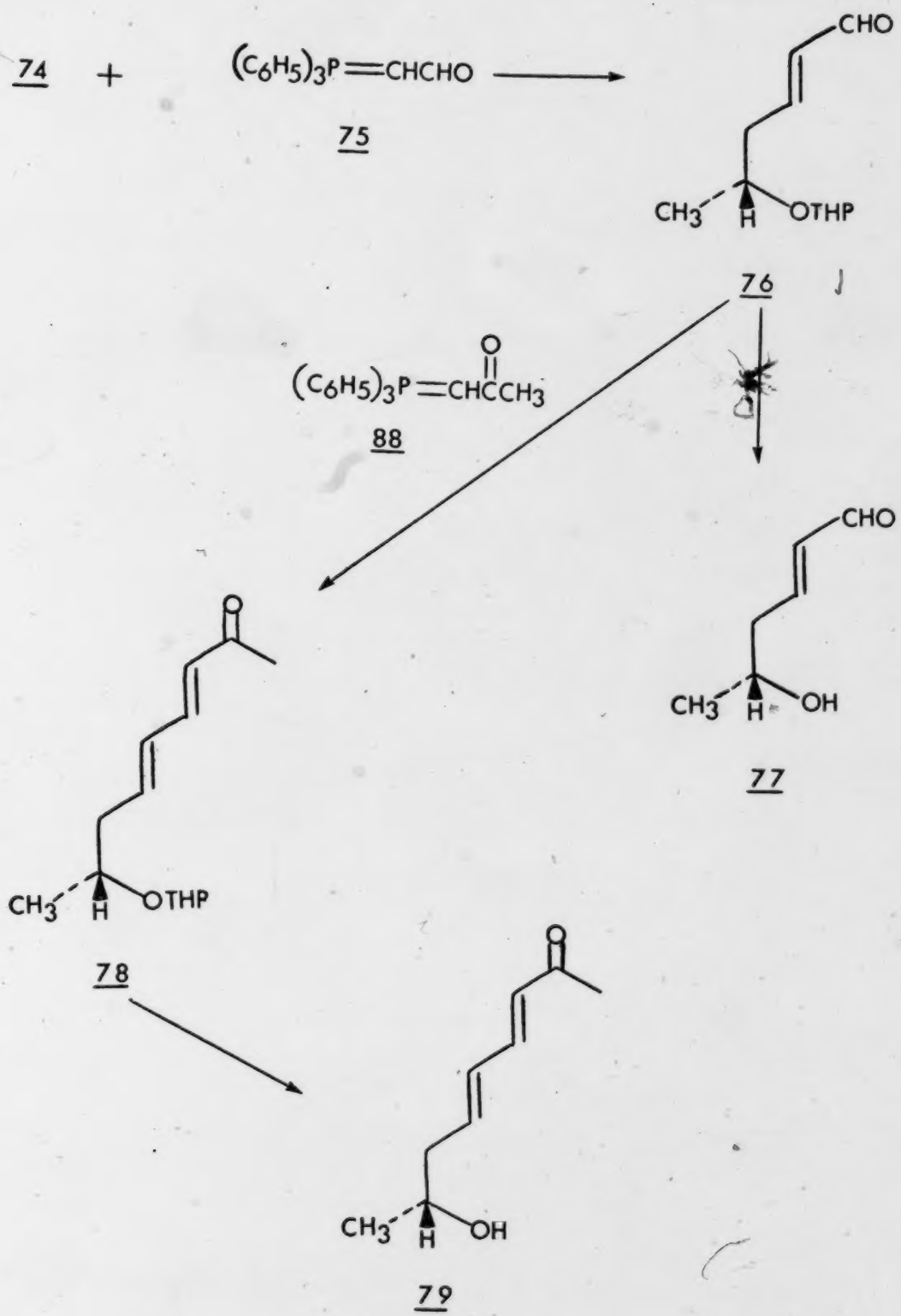


67 68 69

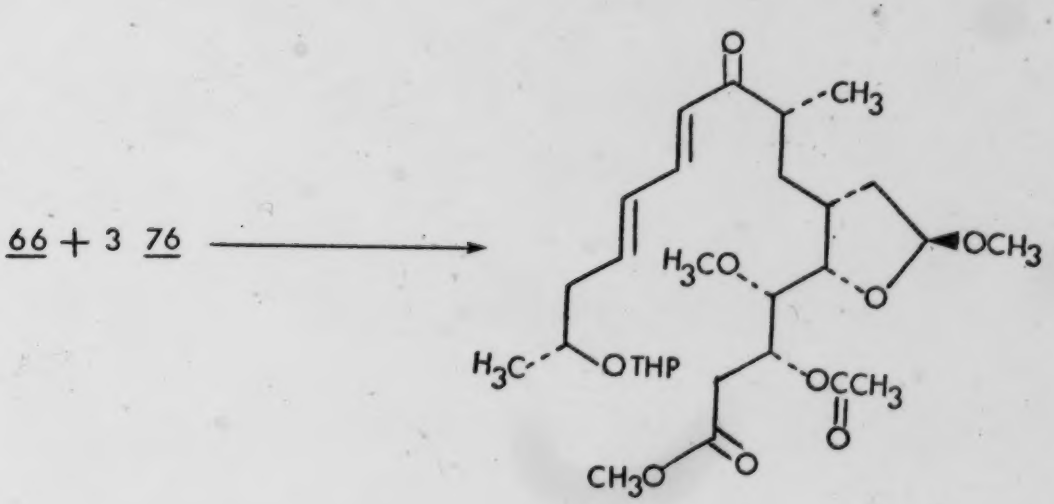
This acid was sufficiently pure for subsequent transformations. Resolution of 69 was accomplished by reaction with quinine in acetone. The yield of the precipitated D(-)-salt was 28% based on the dl acid.[109] Suspension of the D(-)-quinine salt in water, followed by acidification gave 69% of D(-)-β-hydroxybutyric acid 70 (based on the quinine salt) after continuous extraction with ether for 12 hours. The optically pure acid 70 was converted to its methyl ester 71 with diazomethane and the alcohol moiety

was protected as its tetrahydropyranyl ether 72. Reduction of 72 with lithium aluminum hydride gave alcohol 73 in 78% yield. Subsequent oxidation with pyridinium dichromate gave 88% of 3R-(2-tetrahydropyranyl)oxybutanal 74. The aldehyde 74 was then reacted with phosphorane 75 to give α,β unsaturated aldehyde 76 in 50% yield. Model compound 78 was prepared by reaction of aldehyde 76 with phosphorane 88. The THP protecting group of this compound was easily removed by treatment with a 9:1 mixture of acetonitrile and methanol containing 1% trifluoroacetic acid, to give compound 79. Subjecting aldehyde 76 to the same conditions gave compound 77. Aldehyde 77 represents the correct optically active C_{11}-C_{15} segment.




74
+
(C6H5)3P=CHCHO
75
CHO
CH3
H
OTHP
76
(C6H5)3P=CHCCH3
O
88
CHO
CH3
H
OH
77
CH3
H
OTHP
78
CH3
H
OH
79

With compound 76 in hand, it was of interest to try an initial experiment. When phosphorane 66 was reacted with three equivalents of aldehyde 76 in toluene at 95° for 36 hours, compound 80 was obtained in 20% yield along with starting material after purification by column chromatography. This experiment was performed on 2 mg of 66 and further studies will certainly be necessary to increase the yield of 80.

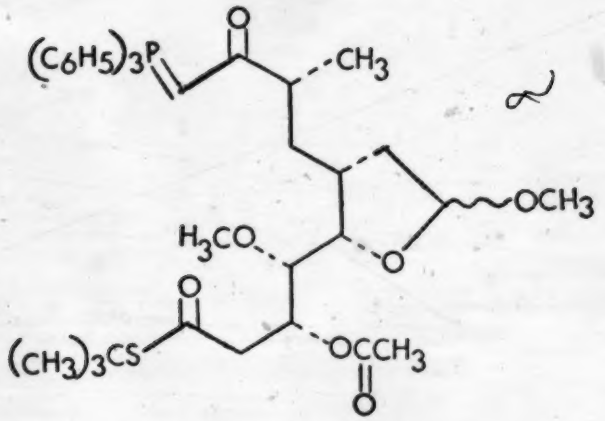


80

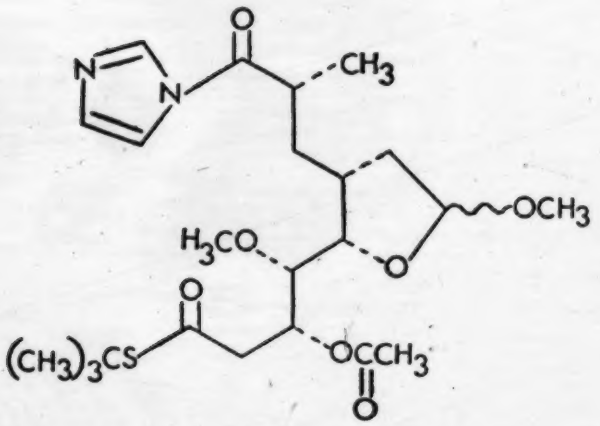
Thus, this synthetic route to the macrolide seems feasible and much of the groundwork for the total synthesis of the aglycone has been laid down. The C_1-C_9 unit has been successfully synthesized with the correct stereochemistry.

Formation of the Wittig reagent 81 via the imidazolide 82, the acid chloride 83 or an equivalent, and subsequent condensation with already synthesized aldehyde 76, would very likely lead to compound 84. As shown with model studies on 78, cleavage of the THP ether protecting group should be facile, leading to the seco-acid 85. The optically active left-hand side would presumably resolve the right-hand side and subsequent cyclization with a "soft" thiophilic metal ion such as mercury, by Masamune's procedure,[80] would give the desired aglycone 86 (which is the aglycone of carbomycin B). The reduction of the C-9 carbonyl has already been reported,[59] thus, reduction with methanolic sodium borohydride gave a 4:1 mixture of natural- and epi-leucomycin A_3 which could be separated to give the aglycone of leucomycin A_3 87. Reaction of carbomycin B 86 with m-chloroperbenzoic acid may give carbomycin A 89. All that would remain is the attachment of the disaccharide unit, which is the same for carbomycin and leucomycin. Fortunately, this has already been accomplished for carbomycin B.[112]

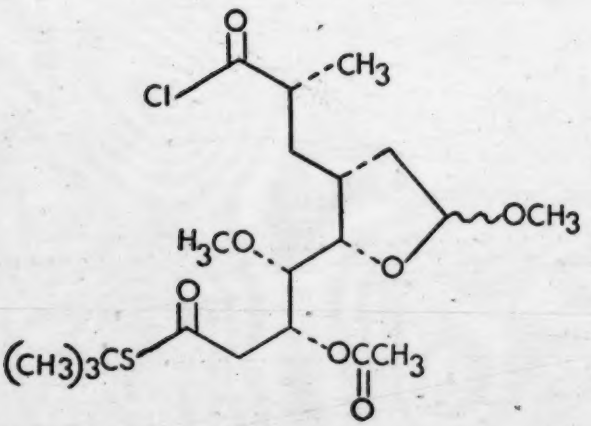
The preparations of compounds 1 to 79 mentioned in this chapter are described in Chapter 5.



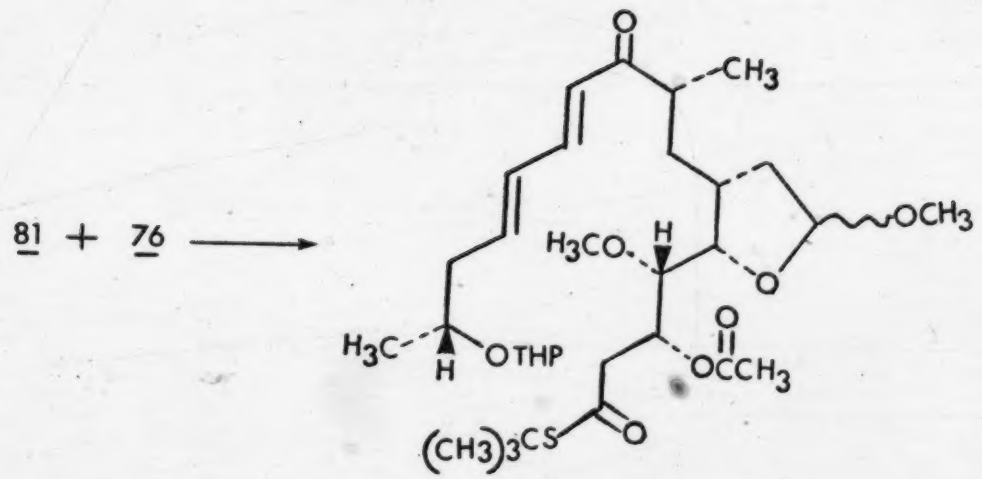
81



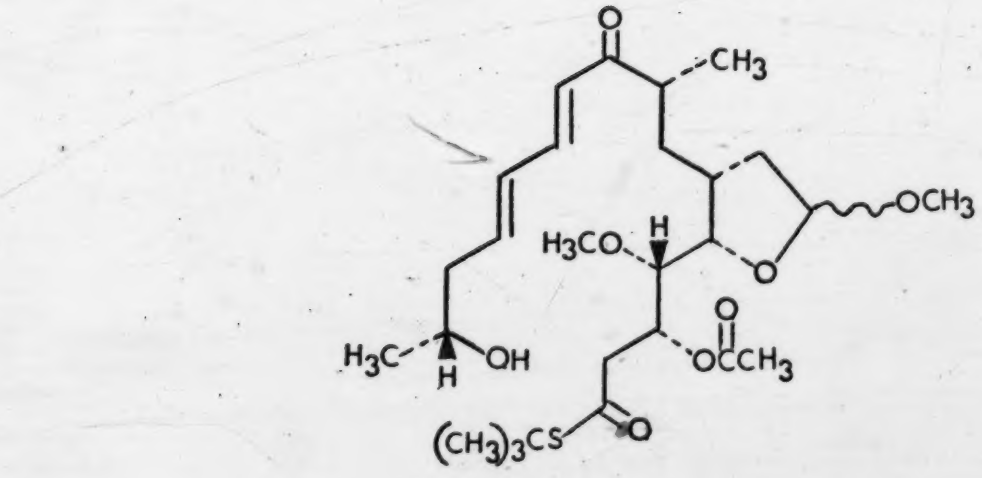
82



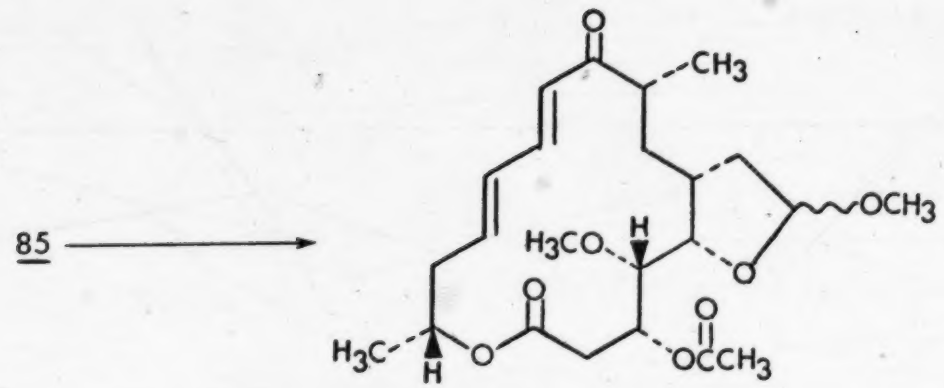
83


81 + 76
CH3
OCH3
H3CO
H
O
H3C
H
OTHP
O
OCCH3
(CH3)3CS
O

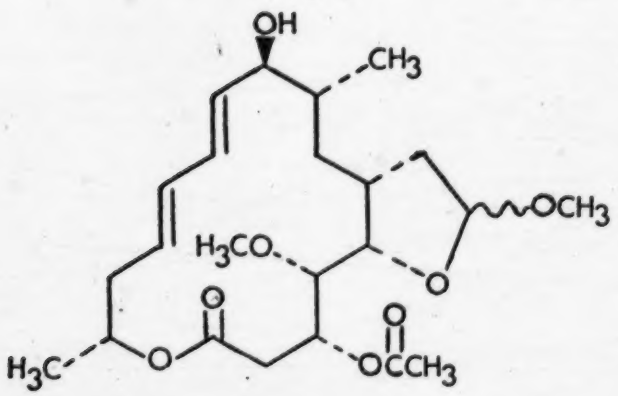
84


CH3
OCH3
H3CO
H
O
H3C
H
OH
O
OCCH3
(CH3)3CS
O

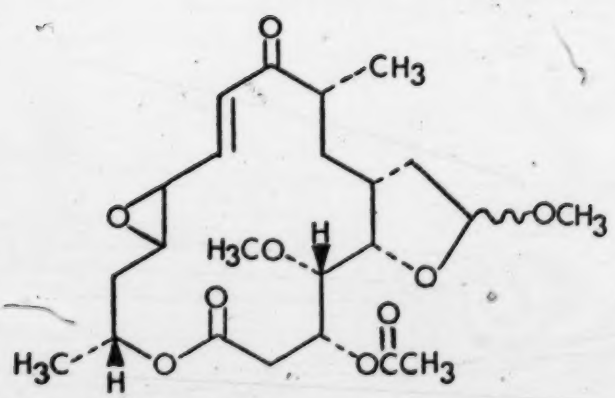
85


85
CH3
OCH3
H3CO
H
H3C
H
OCCH3

86


OH
CH3
OCH3
H3CO
H3C
OCCH3

87


CH3
OCH3
H3CO
H
H3C
H
OCCH3

86

89

CHAPTER 5: EXPERIMENTAL

All boiling points and melting points are uncorrected.

The ^{1}H nmr and ^{13}C nmr spectra were measured with Varian Associates A-60 and/or HA-100 spectrometers and a Bruker HFX-10, WP 200 and/or WP 400 spectrometer respectively. Tetramethylsilane was used as an internal standard unless otherwise specified. All coupling constants are reported in Hz. In reporting ^{1}H nmr spectral data, the following abbreviations are used:

s;	singlet	
d;	doublet	
t;	triplet	
q;	quartet	
quin;	quintet	
sept;	septet	
m;	multiplet	
b;	broad	
c;	complex	(one or more small couplings which overlap the main splitting)

The ir spectra were measured with a Perkin-Elmer Model 257 infrared spectrometer. In reporting ir spectral absorptions, the following abbreviations are used:

s; strong

m; medium

w; weak

b; broad

The mass spectra were measured with an A.E.I. MS-9 and MS-12 spectrometer.

The glpc analyses were performed on a Hewlett-Packard Model 7620 research chromatograph equipped with 1.8 m x 0.3 cm columns (packing reported in the text) and a flame ionization detector.

All reactions were carried out under a dry argon atmosphere. A rotary evaporator (water aspirator) was used for the removal of solvents from all reaction mixtures unless otherwise specified.

Bisfumaronitrile Nickel(0)

The reaction was carried out in a fume hood due to the toxicity of the nickel(0) tetracarbonyl. The procedure followed was that reported by Schrauzer.[87]

Nickel(0) tetracarbonyl (ca. 5 ml, 38 mM) was added to a solution of fumaronitrile (2.0 g, 25 mM) in anhydrous acetone (30 ml). The orange-red mixture was refluxed (dry ice condenser) for 6 hours after which the reaction mixture was stirred at room temperature for 18 hours in order to allow the excess nickel(0) tetracarbonyl to evaporate. The red-brown pyrophoric complex was collected by filtration (in an argon-filled glove bag) through Celite to give 5.4 g (98%) of product which was used directly in the subsequent dimerization of norbornadiene.

Pentacyclo[8.2.1.1.^{4,7}0.^{2,9}0.^{3,8}]tetradecanes (1-3)

Caution! The procedure that follows is a slightly modified version of that reported by Schrauzer and co-workers[88] who carried out this reaction in a sealed tube. For large scale reactions, we do not recommend this method unless the reaction vessel is placed inside a heavy-walled steel apparatus. The reaction mixture exploded several times, resulting in extensive damage to the fume hood, even though the surroundings were protected from the reaction mixture by a safety shield, during the initial experiments.

A mixture of bicyclo[2.2.1]nona-2,5-diene (375 g, 4.1 M), bisfumaronitrile nickel(0) (10.5 g, 50 mM), and triphenyl phosphine (42 g, 160 mM) was added to an argon-purged pressure bottle (ca. 1 L capacity, 5 mm thick walls). The bottle was cooled to 0° and sealed. The bottle was then placed inside a stainless steel hydrogenation apparatus and the reaction heated to 100°. After 48 hours the reaction was cooled to room temperature and the hydrogenation apparatus opened (Note 1). The pressure bottle was cooled in an ice bath, opened, and pentane (400 ml) added to the flask. After shaking, filtering through Celite, and washing the filter pad with pentane (2 x 250 ml), the combined filtrate was concentrated to yield 350 g of dark brown oil. Distillation of the residue gave 285 g (76%) of

a colorless mixture of dimers (bp 60°, 0.3 mm) consisting mostly (ca. 80%) of the endo-anti-exo isomer 2 as estimated by glpc.

The dimeric mixture was formerly available through Aldrich Chemical Company Inc. The ^{1}H nmr spectra of the commercial product and our synthetic dimer are identical.

PHYSICAL DATA FOR 2

bp:	60°, 0.3 mm
ir (CCl_4):	3060 (s), 2960 (s), 1645 (w), 1460 (m), 710 (s)
^{1}H nmr ($CDCl_3$):	δ 0.90-1.52 (m, 4H), 1.53-2.12 (m, 4H), 2.48-2.92 (m, 4H), 5.84-6.44 (m, 4H)
Mass Spectrum:	calcd for $C_{14}H_{16}$: m/e = 184.1252
	measured: m/e = 184.1255
glpc:	Reoplex, 140°

NOTE 1

Even inside the steel apparatus, half of the time the glass vessel exploded, therefore a safer method for the dimerization is reported.

Dimerization of Norbornadiene

This procedure is much safer and provides satisfactory results using an open system. To a magnetically stirred solution of norbornadiene (500 g, 5.45 M) in dry benzene (2 L) fitted with a condenser was added nickel carbonyl (165 ml, 215 g, 1.25 M) over 30 minutes. The mixture was heated at 65° for 24 hours and an additional 55 ml of nickel carbonyl was added quickly in one portion. The temperature was raised to 70° and heating continued for an additional 24 hours. The condenser was removed and the apparatus set up for distillation at atmospheric pressure. In this manner, the solution volume was reduced to ca. 600 ml. On occasion, the mixture turned black and deposited a nickel mirror on the walls of the flask. To the residue was added hexane (1600 ml) and the mixture stirred at room temperature for 2 hours. The dark mixture was filtered through Celite to give a yellow solution which was washed with aqueous 3 N nitric acid (250 ml), aqueous 5% sodium hydroxide (250 ml), and aqueous saturated sodium chloride (250 ml). Drying ($MgSO_4$) and evaporation of solvent gave a yellow oil which upon distillation (65-70°, 0.4 mm) afforded 350 g (70%) of the dimeric mixture (mainly endo-anti-exo as estimated by glpc).

The ^1H nmr of this dimer was identical with the one obtained by the preceding procedure.

Bicyclo[4.2.1]nona-2,4,7-triene (4)

A brief account of this preparation has been reported by Cannell.[90]

The pyrolysis of the norbornadiene dimers was carried out using a flow system. The cracking column was a pyrex tube (2.5 x 35 cm) with a single row of Vigreux indentations at the base. A few millimeters of glass helices were added to the column to support the glass beads that were then added to the column. The column was placed vertically into a Lindberg Hevi-Duty pyrolysis oven. A flow of 40 ml per minute of argon was maintained and the oven heated to 360° (Note 1). The dimeric norbornadiene mixture (consisting mostly of the endo-anti-exo isomer 2) was introduced by means of a Hershberg dropping funnel at a constant rate (one drop every 12-15 seconds) into an argon stream at the top of the pyrolysis column and passed downwards through the pyrolysis column into a three-necked receiving flask cooled at -35°. The pyrolysate was transferred to a round-bottom flask and concentrated (20°, 10 mm) to remove cyclopentadiene. The remaining oil was fractionally distilled through a 30 cm Vigreux column to give triene 4 (bp 50-52°, 15 mm) as a nearly colorless oil in 75% yield.

PHYSICAL DATA FOR 4

bp:	50-52°, 15 mm

ir ($CHCl_3$): 2940 (s), 1720 (bm), 1680 (m), 1450 (w)

^1H nmr ($CDCl_3$): δ 1.30 (d, J_d=11.5, 1H), 1.95 (dt, J_d=11.5, J_t=6, 1H), 3.08 (bt, 2H), 5.44-5.72 (m, 2H), 5.76-6.28 (m, 4H)

Mass Spectrum: calcd for C_9H_{10}: m/e = 118.0782
measured: m/e = 118.0775

glpc: Reoplex, 110°

NOTE 1

The product distribution is a function of both temperature and contact time therefore early fractions should be analyzed by ^1H nmr spectroscopy to find optimum conditions. Over-pyrolysis results in aromatic products (δ7.75); under-pyrolysis in tricyclic diene 6 (δ2.4).

(±)-exo-Bicyclo[4.2.1]nona-2,4-dien-7-ol (7)

The procedure described by Hooz[91] was followed for the preparation of bis(3-methyl-2-butyl) borane.

A solution of 2-methyl-2-butene (70 g, 1.0 M) in anhydrous tetrahydrofuran (100 ml) was added dropwise over 30 minutes to a cold (5°), stirred solution of diborane (0.95 M, 540 ml, 500 mM) in tetrahydrofuran. The solution of dialkylborane was stirred for 3 hours at 5° and then added dropwise over 35-45 minutes to a cold (0-5°), stirred solution of bicyclo[4.2.1]nona-2,4,7-triene 4 (55 g, 466 mM) in anhydrous tetrahydrofuran (150 ml). After the addition was complete, the mixture was stirred at 5° for 2 hours, and then at room temperature for 18 hours. The reaction mixture was then cooled to 5° and hydrolyzed by first adding aqueous 3 N sodium hydroxide solution (175 ml, 525 mM) in several portions and then aqueous 30% hydrogen peroxide (160 ml, 1.5 M). Since the reaction was exothermic, care was taken to add the hydrogen peroxide at such a rate that the temperature of the reaction mixture remained between 30° and 40°. The resulting cloudy mixture was vigorously stirred for 2 hours at room temperature and then extracted with ether (3 x 350 ml). The combined ether extract was washed with water (350 ml) and aqueous saturated sodium chloride (350 ml), dried (Na_2SO_4), and the solvent

evaporated. The residue was distilled at atmospheric pressure to remove the 3-methyl-2-butanol (bp 110-115°, 760 mm) and the remaining oil was fractionally distilled to give 47.6 g (75%) of 7 as a low melting crystalline solid (bp 64-70°, 0.2 mm).

PHYSICAL DATA FOR 7

ir (CCl_4):	3610 (m), 3320 (bm), 3020 (m), 1600 (w), 1030 (s)
^1H nmr ($CDCl_3$):	δ 1.52-2.62 (m, 5H), 2.74 (m, 1H), 3.80 (bs, 1H), 4.25 (m, 1H), 5.48-6.24 (m, 4H)
Mass Spectrum:	calcd for $C_9H_{12}O$: m/e = 136.0888 measured: m/e = 136.0886
Elemental Analysis:	calcd for $C_9H_{12}O$: C 79.37, H 8.88, O 11.75 found: C 79.59, H 8.41, O 11.96
glpc:	Reoplex, 170°

Aluminum tri-*tert*-butoxide

The procedure reported in *Organic Syntheses*[92] was followed. The *tert*-butyl alcohol was distilled from calcium oxide.

Mercury(II) chloride (*ca*. 1 g) was added with vigorous shaking to a gently refluxing mixture of aluminum foil (128 g, 4.74 g-atoms) which had been crumpled into small, loose spheres, *tert*-butyl alcohol (400 g, 510 ml, 5.4 M) and aluminum triisopropoxide (10 g). The reaction mixture turned white, and then black over 1-2 hours, after which time the heat source was removed and *tert*-butyl alcohol (488 g, 620 ml, 6.6 M) and anhydrous benzene (400 ml) were added. The reaction subsided at this point, but was reactivated again with gentle heating. The mixture continued to reflux without external heating for *ca*. 2 hours and then was heated at reflux for 18 hours. The benzene and excess *tert*-butyl alcohol were removed by distillation and anhydrous ether (*ca*. 2000 ml) was added. The mixture was briefly refluxed to dissolve the product, and after the solution had cooled to room temperature, wet ether (75 ml) was added, followed by vigorous shaking. The mixture was allowed to stand for 2 hours and was then centrifuged. After decanting the supernatant ether, the residual solvent was evaporated and the product was finely ground, and then dried for 5 hours under reduced pressure (0.01 mm) to give 780 g (80%) of a light grey powder.

(±)-Bicyclo[4.2.1]nona-2,4-diene-7-one (8)

Oppenauer Oxidation

Commercial 98% 4-benzoquinone was used without further purification. The quinone must be bright yellow in color. If it appears slightly greenish, it must be recrystallized from hexane or sublimed prior to use. The procedure followed was that outlined by Wiberg et al.[93] and Bly and Bly[94] with some modifications.

Finely powdered aluminum tri-tert-butoxide (150 g, 610 mM) was added to a solution of exo-alcohol 7 (75 g, 550 mM) and 4-benzoquinone (265 g, 2.45 M) in anhydrous ether (3.2 L). When heated to reflux, the solution immediately became purple and a precipitate formed. After refluxing for 24 hours, the mixture was cooled to room temperature and slowly hydrolyzed with cold aqueous 3 N hydrochloric acid (500 ml). The ether layer was decanted, and the aqueous phase was extracted with a further 750 ml of ether. The combined ether layer was washed with aqueous 3 N hydrochloric acid (4 x 250 ml), aqueous 1 N sodium hydroxide (6 x 250 ml or until the ether layer was almost colorless), and aqueous saturated sodium chloride (2 x 250 ml). The ether was evaporated, and the residue was dissolved in dichloromethane (500 ml) and dried (Na_2SO_4). Evaporation of the solvent at 5° and short-path distillation of

the remaining yellow oil gave 55.3 g (75%) of the desired ketone 8 (bp 50°, 0.4 mm). A more efficient procedure for this oxidation follows.

The procedure utilizes the method reported by Omura and Swern.[95]

To a mechanically stirred solution of dimethylsulfoxide (distilled from calcium hydride) (56 ml, 0.8 M) in dry dichloromethane (400 ml) cooled to -65°, was added dropwise a solution of trifluroacetic anhydride (84 ml, 0.6 M) in dichloromethane (200 ml) over a period of ca. 30 minutes, keeping the temperature below -65°. The mixture was stirred at this temperature for 15 minutes and then a solution of exo alcohol 7 (54 g, 0.4 M) in dichloromethane (200 ml) was added dropwise over ca. 30 minutes, again maintaining the temperature below -65°. Stirring was continued for 30 minutes, and then triethylamine (160 ml) was added while maintaining the temperature below -65° until completion of addition, and then the cooling bath was removed and the mixture allowed to warm to room temperature. The dichloromethane was evaporated, the solution diluted with hexane (600 ml), and the hexane layer was washed with aqueous 1 N sulphuric acid (300 ml). The aqueous layer was then back extracted with hexane (100 ml) and the combined organic layers were washed with aqueous 1 N sulphuric acid (150 ml), aqueous 5% sodium hydroxide (2 x 150 ml), aqueous saturated

sodium chloride (150 ml), dried (Na_2SO_4), and the solvent evaporated. Short-path distillation of the residue gave 50 g (94%) of the desired ketone 8 as a colorless oil.

PHYSICAL DATA FOR 8

ir (CCl_4):	3044 (m), 1750 (s), 1595 (m)
^1H nmr ($CDCl_3$):	δ 1.84 (dd, J_d=12.5, J_d=1.6 1H), 2.00-2.59 (m, 3H), 2.90 (m, 1H), 3.27 (m, 1H), 5.38-6.33 (m, 4H)
Mass Spectrum:	calcd for $C_9H_{10}O$: m/e = 134.0732
	measured: m/e = 134.0728
glpc:	Reoplex, 170°

(±)-Bicyclo[4.2.1]nona-3-formyl-5,7-dien-2-one (9)

The procedure followed was similar to that reported by Ainsworth.[96] Ethyl formate was distilled from phosphorous pentoxide.

A solution of ketone 8 (62.5 g, 465 mM) and ethyl formate (60 ml, 54.5 g, 735 mM) in anhydrous ether (100 ml) was added dropwise over 30 minutes to a cold (5°), stirred suspension of sodium hydride (50% dispersion in mineral oil, 50 g, 1.04 M) and 98% ethanol (4 ml) in anhydrous ether 1.2 L). The reaction mixture was stirred for 14 hours; then treated with a further portion of 98% ethanol (20 ml) and after an additional 1 hour stirring, water (400 ml) was added to the reaction mixture. After a few minutes, two homogeneous layers formed. The layers were separated and the ether layer washed with water (3 x 250 ml). The combined aqueous layer was washed with ether (3 x 250 ml), cooled to 5°, mixed with dichloromethane (600 ml), and finally acidified to pH 1-2 with aqueous 3 N hydrochloric acid. The dichloromethane layer was separated and the aqueous solution extracted with dichloromethane (3 x 400 ml). The combined dichloromethane extracts were dried (Na_2SO_4), and the solvent evaporated to give 64.0 g (85%) of crude 9 as a pink solid (mp 111-115°). This product was used in the subsequent reaction without further purification.

PHYSICAL DATA FOR 9

ir ($CHCl_3$): 3600-2500 (bm), 1673 (s), 1600 (s)

^1H nmr ($CDCl_3$): δ 1.75 (d, J_d=12, 1H), 2.14-2.68 (m, 1H), 3.45 (bt, 2H), 5.55-6.56 (m, 4H), 7.30 (s, 1H), 8.95 (bs, 1H)

cis-Cyclohepta-4,6-diene-1,3-dicarboxylic acid (10)

The methodology for the oxidative cleavage of a 1,3-dicarbonyl system by means of the periodate oxidation was reported by Cornforth, Cornforth and Popjack[97] and was followed with certain modifications.

A solution of sodium metaperiodate (121 g, 568 mM) in water (800 ml) was added rapidly to a cold (0-5°), stirred solution of the crude hydroxymethylene ketone 9 (30.2 g, 186 mM) in dioxane (400 ml). After completion of the addition of the periodate solution, the cold reaction mixture was diluted with water (800 ml). Stirring and cooling were maintained for 1 hour during which time aqueous 3 N sodium hydroxide (130 ml) was added dropwise to maintain the pH of the reaction at 4.5-5.0. A white precipitate formed during the 1 hour period, after which time the ice bath was removed and the mixture stirred at room temperature for 4.5 hours. The mixture was filtered through Celite and the filter pad was washed with dioxane (2 x 200 ml). The combined filtrate was concentrated to about 1 L on the rotary evaporator while keeping the water bath at 35-40°. The residue was acidified to pH 1-1.5 with aqueous 2 N sulphuric acid, saturated with sodium chloride and extracted with ether (5 x 500 ml). The ether layer was washed with aqueous saturated barium carbonate (250 ml) to remove residual sulphuric acid, and then with aqueous saturated sodium chloride (250 ml). The ether solution was dried

($MgSO_4$) and evaporated to give a brown solid which was suspended in dichloromethane (100 ml) and filtered to give 26.0 g (78%) of diacid 10 as a tan solid. A ^1H nmr spectrum of the dimethyl ester of the diacid showed no signals attributable to the trans isomer.[98]
An analytical sample was recrystallized from ether-hexane.

PHYSICAL DATA FOR 10

mp:	286-289°, decomp
ir (paraffin oil):	3400-2100 (bs), 1680 (bs), 1280 (bs)
^1H nmr (acetone-d6):	δ 1.78-2.48 (m, 2H), 3.02-3.38 (m, 2H), 5.34-5.66 (m, 4H), 9.12 (bs, 2H)
Elemental Analysis:	calcd for $C_9H_{10}O_4$: C 59.33, H 5.54, O 35.13
	found: C 59.39, H 5.62, O 35.01

Diazomethane

N-Methyl-N-nitrosourea (25.8 g, 250 mM) was added in small portion to a gently stirred mixture of ether (250 ml) and aqueous 50% potassium hydroxide (87.5 g in 87.5 ml of water) over 1.5 hours at 0-5°. The yellow ether layer was decanted onto potassium hydroxide pellets and stored at -20° for at least 3 hours. The diazomethane concentration (0.4-0.5 M) was determined prior to use by reaction of an aliquot of solution with excess benzoic acid, followed by back titration of the remaining acid with aqueous 0.1 N sodium hydroxide.

Dimethyl cis-Cyclohepta-4,6-diene-1,3-dicarboxylate (11)

Methanol was added dropwise to a suspension of diacid 10 (100 mg, 0.55 mM) in ether (2 ml) until the acid just dissolved. Treatment with excess ethereal diazomethane and evaporation of solvent left an oil which was dissolved in dichloromethane (2 ml) and dried ($MgSO_4$). Evaporation of the solvent gave 114 mg (99%) of 11 as a colorless oil. A ^1H nmr spectrum did not show any signals due to the trans-diester.[98]

PHYSICAL DATA FOR 11

ir ($CHCl_3$): 1742 (s), 1438 (m)

^1H nmr ($CDCl_3$): δ 2.28 (dt, J_d=13.0, J_t=12.0, 1H), 2.62 (dt, J_d=13.0, J_t=3.0, 1H), 3.48 (cd, J=5, 2H), 3.70 (s, 6H), 5.72-6.08 (m, 4H)

glpc: UCW-98, 185°

4-Methoxy-7-oxo-6-oxabicyclo-[3.2.2]non-2-ene-9-carboxylic acid (12)

A solution of diacid 10 (3.0 g, 16.5 mM) and m-chloroperbenzoic acid (3.36 g, 16.5 mM) in dry methanol (60 ml) was stirred for approximately 48 hours (until the solution gave a negative test with starch-iodide paper), and an additional 24 hours at reflux temperature. After removal of solvent, the residue was chromatographed on silica gel (120 g) using hexane as eluent and gradually increasing to 3:1 hexane:ethyl acetate to give 1.63 g (47%) of an oily residue. Although not totally pure, this acid was sufficiently pure for the next step. The polar by-product 1 gm (34%) thought to be 13 was obtained as a white crystalline material.

PHYSICAL DATA FOR 12

mp: 101-102°

ir ($CHCl_3$): 3500-2500 (bs), 1755 (s), 1715 (s)

^1H nmr ($CDCl_3$): δ 2.42 (m, 2H), 3.12-3.38 (m, 2H), 3.46 (s, 3H), 4.18 (m, 1H), 5.16 (m, 1H), 5.85 (m, 2H), 10.50 (bs, 1H)

Mass Spectrum: ($^m/_e$ intensity assignment)
212 (M^+, 2%), 184 (M^+-CO, 100%)

Elemental Analysis: calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70, O 37.70

found: C 56.32, H 5.75, O 37.76

PHYSICAL DATA FOR 13

mp: 130-132°

ir ($CHCl_3$): 3200 (bm), 1754 (s), 1701 (s)

^1H nmr (acetone-d6): δ 1.64-2.78 (m, 3H), 3.36 (td, J_t=6.5, J_d=2.0, 1H), 4.01 (dd, J_d=10.0, J_d=2.0, 1H), 4.90 (ddt, J_d=4.5, J_d=2.0, J_t=2.0, 1H), 6.26-6.62 (m, 2H), 7.0 (bm, 2H)

Methyl 4-Methoxy-7-oxo-6-oxabicyclo-[3.2.2]non-2-ene-9-carboxylate (14)

Methanol was added to a suspension of acid 12 (21.2 mg, 0.1 mM) in ether (0.5 ml) until the acid just dissolved. After treatment with excess ethereal diazomethane, the solvent was evaporated, the oil dissolved in dichloromethane (2 ml) and the solution dried (Na_2SO_4). Evaporation of solvent gave 22.5 mg (100%) of 14 as a white solid.

PHYSICAL DATA FOR 14

mp:	108-109°
ir (CCl_4):	1772 (s), 1747 (s)
^1H nmr ($CDCl_3$):	δ 2.42 (m, 2H), 3.28 (m, 2H), 3.48 (s, 3H), 3.76 (s, 3H), 4.16 (m, 1H), 5.14 (m, 1H), 5.64-6.08 (m, 2H)
Mass Spectrum:	calcd for $C_{11}H_{14}O_5$: m/e = 226.0841
	measured: m/e = 226.0838
Elemental Analysis:	calcd for $C_{11}H_{14}O_5$: C 58.40, H 6.24, O 35.36
	found: C 58.11, H 6.22, O 34.98

4-Methoxy-7-oxo-6-oxabicyclo[3.2.2] non-2-ene-9-carboxylic acid chloride (15)

To the crude acid 12 (3.36 g, 15.9 mM) was added dry benzene (100 ml) and oxalyl chloride (5 ml, 57.4 mM). The mixture was stirred over night and the solvent removed to give 3.65 g (100%) of white solid. After confirmation of the acid chloride formation by infrared analysis, the acid chloride was used directly in the next step.

PHYSICAL DATA FOR 15

mp: 51-54°

ir (CCl_4): 1780 (bs), 1740 (bs)

^1H nmr ($CDCl_3$): δ 2.42 (m, 1H), 2.58 (m, 1H), 3.26 (m, 1H), 3.52 (s, 3H), 3.72 (m, 1H), 4.20 (m, 1H), 5.16 (m, 1H), 5.78 (m, 1H), 5.95 (m, 1H)

4-Methoxy-7-oxo-6-oxa-9-(1-oxo-2-diazoethyl)-bicyclo[3.2.2]non-2-ene (16)

The crude acid chloride 15 (3.65 g, 15.9 mM) was dissolved in dry benzene (30 ml) and then added dropwise to a stirred solution of diazomethane in ether (0.42 M, 85 ml, 35 mM). The mixture was stirred at room temperature for 14 hours and the solvent removed. The residue was purified by column chromatography on silica gel (120 g) using hexane as eluent and changing gradually to a 1:1 mixture of hexane and ethyl acetate to give 3.35 g (90%) of a brownish yellow solid. Suspending in ether and filtering gave 3.05 g (82%) of bright yellow crystals.

PHYSICAL DATA FOR 16

mp: 108-109°

ir ($CHCl_3$): 2120 (s), 1760 (s), 1650 (s)

^1H nmr ($CDCl_3$): δ 2.24 (dd, J_d=3.0, J_d=9.0, 2H), 3.1-3.36 (m, 2H), 3.48 (s, 3H), 4.16 (m, 1H), 4.96 (m, 1H), 5.32 (s, 1H), 5.66-6.08 (m, 2H)

Mass Spectrum: calcd for $C_{11}H_{12}N_2O_4$: m/e = 236.0797
found: m/e = 236.0795

Elemental Analysis: calcd for $C_{11}H_{12}N_2O_4$: C 55.93, H 5.12, O 27.09, N 11.86

found: C 55.81, H 5.16, O 27.56, N 11.84

4-Methoxy-7-oxo-6-oxabicyclo-[3.2.2]non-2-ene-9-acetic acid (17)

A solution of diazoketone 16 (200 mg, 0.845 mM) in wet (10%) tetrahydrofuran (75 ml) was photolyzed under argon with a 450 W medium pressure Hanovia lamp through a pyrex filter for 3 hours. The solution was evaporated to dryness and any remaining water removed by benzene azeotrope to give quantitative yield of the acid. Recrystallization from ethyl acetate gave 182 mg (95%) of white crystals.

PHYSICAL DATA FOR 17

mp:	125-126°
ir ($CHCl_3$):	3500-2800 (b), 1755 (s), 1715 (s)
^1H nmr ($CDCl_3$):	δ 1.42-3.22 (m, 6H), 3.43 (s, 3H), 4.12 (m, 1H), 4.51 (dd, J_d=5, J_d=2, 1H), 5.56-6.12 (m, 2H), 7.5 (bs, 1H)
Mass Spectrum:	calcd for $C_{11}H_{14}O_5$: m/e = 226.0841 measured: m/e = 226.0846
Elemental Analysis:	calcd for $C_{11}H_{14}O_5$: C 58.40, H 6.24, O 35.36 found: C 58.49, H 6.36, O 35.45

4-Methoxy-7-oxo-6-oxabicyclo-[3.2.2]non-2-ene-9-acetic acid carboxylate (18)

Methanol was added to a suspension of acid 17 (22.6 mg, 0.1 mM) in ether (0.5 ml) until the acid just dissolved. After treatment with excess ethereal diazomethane, the solvent was evaporated, the oil dissolved in dichloromethane (2 ml) and dried (Na_2SO_4). Evaporation of solvent gave 23.9 mg (100%) of 18 as an oil.

PHYSICAL DATA FOR 18

ir (CCl_4): 1770 (s), 1745 (s)

^1H nmr ($CDCl_3$): δ 1.42-2.96 (m, 6H), 3.44 (s, 3H), 3.72 (s, 3H), 4.12 (m, 1H), 4.52 (m, 1H), 5.60-6.02 (m, 2H)

4-Methoxy-7-oxo-6-oxa-9-(2-hydroxyethyl)bicyclo[3.2.2]non-2-ene (19)

To a solution of the acid 17 (2.26 g, 10 mM) in dry tetrahydrofuran (120 ml) at 0° was added triethylamine (1.6 ml, 11.2 mM) and ethyl chloroformate (1.07 ml, 11.3 mM) and the resulting mixture stirred at 0° for 30 minutes. Sodium borohydride (1.58 g, 40 mM) and isopropanol (4 ml) were then added and the mixture stirred for an additional 15 minutes. Water was added slowly until gas evolution ceased, and then the mixture was warmed to room temperature. The volume was increased to 250 ml with water and the aqueous solution extracted with chloroform (3 x 200 ml). The combined organic layers were washed with aqueous saturated sodium chloride, dried (Na_2SO_4) and evaporated to give 2.1 g of oil. This oil was kept on a vacuum pump for 48 hours to remove less volatile components to give 2.02 g (90%) of 19 as a colorless oil.

PHYSICAL DATA FOR 19

ir ($CHCl_3$): 3480 (s), 1750 (s)

^1H nmr ($CDCl_3$): δ 1.48-3.22 (m, 7H), 3.44 (s, 3H), 3.68 (t, J_t=6.5, 2H), 4.10 (m, 1H), 4.52 (dd, J_d=2, J_d=4, 1H), 5.62-6.00 (m, 2H)

Mass Spectrum: ($\frac{m}{e}$ intensity assignment)

212 (M^+, 4%), 184 (M^+-CO, 100%),

166 (M^+-CO-H_2O, 20%)

glpc: UCW-98, 240°

4-Methoxy-7-oxo-6-oxa-9-(3,5-dioxahexyl)-bicyclo[3.2.2]non-2-ene (20)

Some of the properties of the methoxymethyl protecting group are reported in Chapter 3, Part II.

To a solution of alcohol 19 (1.8 g, 8.16 mM) in dry dichloromethane (50 ml) was added diisopropylethylamine (1.43 ml, 8.22 mM) and then chloromethyl methyl ether (0.625 ml, 8.22 mM). The mixture was stirred for 12 hours, transferred to a separatory funnel and washed with dilute aqueous hydrochloric acid (pH=3, 2 x 50 ml), water (25 ml), aqueous saturated sodium chloride, dried (Na_2SO_4) and the solvent evaporated. Purification by column chromatography over silica gel (40 g) using hexane as eluent and increasing to a 1:1 mixture of hexane and ethyl acetate gave 1.98 g (91%) of 20 as a colorless oil.

PHYSICAL DATA FOR 20

ir ($CHCl_3$): 1750 (s)

^1H nmr ($CDCl_3$): δ 1.48-1.94 (m, 3H), 2.14-2.84 (m, 2H), 3.12 (m, 1H), 3.34 (s, 3H), 3.44 (s, 3H), 3.56 (t, J_t=6, 2H), 4.10 (m, 1H), 4.48 (dd, J_d=2, J_d=4, 1H), 4.58 (s, 2H), 5.62-6.00 (m, 2H)

(±)-3S-Methoxy-4S-hydroxy-5R-(3,5-dioxahexyl)-7R-hydroxymethyl-cyclohept-1-ene (21)

A solution of lactone 20 (1.9 g, 7.42 mM) in dry tetrahydrofuran (50 ml) was added dropwise over 15 minutes to a suspension of lithium aluminum hydride (0.646 g, 17.03 mM) in anhydrous tetrahydrofuran (150 ml). The mixture was stirred for 30 minutes and then aqueous saturated sodium sulphate was added dropwise until the excess hydride was consumed. The mixture was filtered through Celite and the filter pad washed well with hot tetrahydrofuran. The solution was evaporated and the remaining water removed by azeotrope with benzene. The residue was taken up in chloroform (50 ml) and dried (Na_2SO_4). Evaporation of solvent gave 1.89 g (98%) of 21 as a colorless oil.

PHYSICAL DATA FOR 21

ir (CCl_4): 3460 (bs)

^{1}H nmr ($CDCl_3$): δ 1.12-2.80 (m, 8H), 3.34 (s, 3H), 3.37 (s, 3H), 3.48-3.72 (m, 4H), 3.94 (m, 2H), 4.60 (s, 2H), 5.78 (m, 2H)

(±)-3S-Methoxy-4S-hydroxy-5R-(3,5-dioxahexyl)-7R(4-toluenesulfonyl-oxymethyl)-cyclohept-1-ene (22)

A solution of diol 21 (0.9 g, 3.45 mM), p-toluenesulfonyl chloride (0.65 g, 3.41 mM) and pyridine (30 ml) was stirred at 0° for 12 hours. The solution was concentrated under reduced pressure and taken up in ether (75 ml). The ether solution was cooled to 0° with rapid stirring, cold aqueous 1 N sulphuric acid (50 ml) was added, and the layers separated. The aqueous layer was washed with ether (3 x 20 ml) and the combined organic phase washed with water (40 ml), aqueous saturated sodium chloride (40 ml), dried (Na_2SO_4), and the solvent evaporated to give 1.35 g (94%) of tosylate 22 as an oil.

PHYSICAL DATA FOR 22

ir ($CHCl_3$): 3500 (b)

^1H nmr ($CDCl_3$): δ 1.08-2.90 (m, 7H), 2.44 (s, 3H), 3.30 (s, 3H), 3.32 (s, 3H), 3.56 (t, J_t=6.0, 2H), 3.84 (m, 2H), 3.91 (d, J_d=6.0, 2H), 4.58 (s, 2H), 5.88 (m, 2H), 7.18-7.88 (m, 2H)

(±)-3S-Methoxy-4S-trimethylsilyloxy-5R-(3,5-dioxahexyl)-7R-(4-toluenesulfonyloxymethyl)-cyclohept-1-ene (23)

A solution of tosyloxy alcohol 22 (1.2 g, 2.9 mM), pyridine (20 ml), and trimethylsilylchloride (0.942 ml, 7.3 mM) was stirred for 2 hours at room temperature. The solvent was removed on a vacuum pump and the residue dissolved in ether (50 ml). The ether layer was washed with water (20 ml) and the aqueous layer was back extracted with ether (2 x 20 ml). The combined organic layers were washed with aqueous saturated sodium chloride (20 ml), dried (Na_2SO_4) and the solvent evaporated to give 1.34 g (95%) of 23 as an oil.

PHYSICAL DATA FOR 23

^{1}H nmr ($CDCl_3$): δ ($CHCl_3$ ref.) 0.02 (s, 9H), 1.02-2.92 (m, 6H), 2.44 (s, 3H), 3.26 (s, 3H), 3.32 (s, 3H), 3.51 (t, J_t=6.0, 2H), 3.82 (m, 2H), 3.89 (d, J_d=6.0, 2H), 4.58 (s, 2H), 5.60 (m, 2H), 7.34 (d, J_d=8.0, 2H), 7.80 (d, J_d=8.0, 2H)

(±)-3S-Methoxy-4S-trimethylsilyloxy-5R-(3,5-dioxahexyl)-7R-methylcyclohept-1-ene (24)

A solution of tosylate 23 (1.25 g, 2.6 mM) in anhydrous ether (25 ml) was added dropwise to lithium aluminum hydride (225 mg, 7.25 mM) in anhydrous ether (75 ml) at 0°. The mixture was allowed to warm to room temperature and was stirred for 12 hours. The mixture was quenched with aqueous saturated sodium sulphate solution, filtered through Celite, and the solvent evaporated to give 710 mg (90%) of 24 as an oil.

PHYSICAL DATA FOR 24

^{1}H nmr ($CDCl_3$): δ ($CHCl_3$ ref.) 0.03 (s, 9H), 1.00 (d, J_d=7.0, 3H), 1.20-2.72 (m, 6H), 3.30 (s, 3H), 3.34 (s, 3H), 3.54 (t, J_t=6.0, 2H), 4.04-4.60 (m, 2H), 4.60 (s, 2H), 4.88-5.30 (m, 2H)

(+)-3S-Methoxy-4S-hydroxy-5R (3,5-dioxahexyl)-7R-methyl-cyclohept-1-ene (25)

The trimethylsilyloxy-cycloheptene 24 (320 mg, 1.01 mM) was dissolved in methanol (10 ml) containing a trace amount of trifluroacetic acid and stirred at room temperature for 1 hour. The reaction was monitored by thin layer chromatography. Evaporation of solvent and column chromatography on silica gel (10 g) using hexane:ethyl acetate 1:1 gave 234 mg (96%) of 25 as an oil.

PHYSICAL DATA FOR 25

ir ($CHCl_3$): 3500 (b)

^1H nmr ($CDCl_3$): δ 1.04 (d, J_d=7.0, 3H), 1.20-2.68 (m, 7H), 3.34 (s, 3H), 3.37 (s, 3H), 3.59 (t, J_t=6.0, 2H), 3.88 (m, 2H), 4.60 (s, 2H), 5.64 (m, 2H)

Mass Spectrum: (m/e intensity assignment)
244 (M^+, 0%), 212 (M^+-CH_3OH, 7.21%)

(±)-3S-Methoxy-4S-benzoyloxy-5R (3,5-dioxahexyl)-7R-methyl-cyclohept-1-ene (26)

To a solution of alcohol 25 (116 mg, 0.475 mM) in pyridine (60 μl) was added benzoyl chloride (67 μl, 0.52 mM). The reaction was stirred at room temperature for 30 minutes and the pyridine removed on a vacuum pump. Preparative thin layer chromatography on silica gel plates using chloroform as solvent gave 150 mg (91%) of 26 as an oil.

PHYSICAL DATA FOR 26

ir ($CHCl_3$): 1720 (s)

^1H nmr ($CDCl_3$): δ 1.12 (d, J_d=7.0, 3H), 1.18-2.50 (m, 6H), 3.30 (s, 3H), 3.34 (s, 3H), 3.58 (t, J_t=3.0, 2H), 4.08 (m, 1H), 4.50 (s, 2H), 5.50-5.95 (m, 2H), 7.36- 8.20 (m, 5H)

Oxidizing Reagent

The oxidizing reagent for the Lemieux-von Rudloff oxidation was prepared by dissolving sodium meta-periodate (2.09 g) and potassium permanganate (40 mg) in water and diluting to 100 ml in a volumetric flask. This solution was 0.1 M in periodate.

(±)-2S-Methoxy-3S-benzoyloxy-4R(3,5-dioxahexyl)-6R-methyl-1,7-heptane dicarboxylic acid (27)

The procedure followed was that reported by R. U. Lemieux and E. von Rudloff[99] with some modification.

To a solution of the benzoate 26 (34.8 mg, 0.1 mM) in aqueous 80% tert-butyl alcohol (3 ml) at 0° was added sodium meta-periodate solution (7 ml of 0.1 M solution, 0.7 mM) containing potassium carbonate (15.9 mg, 0.11 mM). The reaction was allowed to warm to room temperature and stirred for an additional 14 hours. After cooling the reaction to 5°, the red-purple solution was acidified to pH 3.0 with aqueous 2 N sulphuric acid. Solid sodium bisulphite was added to reduce the remaining oxidant. During the addition, the solution first became colorless, then dark brown, and finally bright yellow (the pH of the solution was now 1.5). The solution was carefully saturated with sodium chloride (sulphur dioxide from the excess sodium bisulphite was evolved). The solution was extracted with chloroform (4 x 20 ml) and the combined organic layers washed with aqueous saturated sodium chloride (20 ml), dried (Na_2SO_4), and the solvent removed to give 38.6 mg (92%) of 27 as a white amorphous solid.

PHYSICAL DATA FOR 27

ir ($CHCl_3$): 3500-2800 (b), 1720 (bs)

^{1}H nmr ($CDCl_3$): δ 1.22 (bd, J_d=8.0, 3H), 1.30-2.75 (m, 5H), 3.28 (s, 3H), 3.32 (s, 3H), 3.60 (m, 3H), 4.02 (d, J_d=6.0, 1H), 4.52 (s, 2H), 5.48 (m, 1H), 7.26-8.18 (m, 5H), 10.5 (bs, ca. 2H)

(±)-3S-Hydroxy-2R,S-methoxy-4R(3,5-dioxahexyl)-6-R-methyl heptan-1,7-dioic 3,7-lactone (28)

(1) A solution of benzoyloxy-dicarboxylic acid 27 (32 mg, 0.08 mM) in aqueous 1.8 N potassium hydroxide (0.2 ml, 0.36 mM) was stirred at room temperature for 18 hours, then cooled to 0-5° and carefully acidified to pH=3 with aqueous 2 N sulphuric acid. After saturation of the solution with sodium chloride and extraction with ether (3 x 15 ml), the combined ether layers were washed with aqueous saturated sodium chloride (5 ml) and dried (Na_2SO_4). Evaporation of solvent and preparative thin layer chromatography on silica gel plates using chloroform-methanol 95:5 as the solvent system gave 23 mg of a yellowish oil which displayed ^1H nmr characteristics of an epimeric mixture 28.

PHYSICAL DATA FOR 28

^1H nmr ($CDCl_3$): δ 1.22 (bd, J_d=3.0, 2H), 1.43-2.65 (m, 5H), 3.34 (s, 3H), 3.5 (bs, 3H), 3.65 (t, J_t=6.0, 2H), 3.98 (m, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 6.5 (bs, ca. 1.5H)

(2) A solution of benzoyloxy-dicarboxylic acid 27 (32 mg, 0.08 mM) was dissolved in dry methanol (1 ml) containing sodim methoxide (9.9 mg, 0.184 mM) and the mixture was stirred at room temperature for 12 hours. The solvent was evaporated and the remaining white precipitate was dissolved

in cold aqueous 5% sodium bicarbonate (2 ml). The aqueous layer was washed with chloroform (3 x 5 ml) to remove any methyl benzoate and the solution was carefully acidified to pH=3 with aqueous 2 N sulphuric acid at 0-5°. After saturation of the aqueous solution with sodium chloride, the aqueous layer was washed with chloroform (4 x 10 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent gave 22 mg of oil. The ^1H nmr spectrum exhibited mostly characteristics of starting material (estimated 90% from integration) with the signal at δ3.5 broadened.

(+)-3S-Hydroxy-2S-methoxy-4R(3,5-dioxahexyl)-6R-methyl heptan-1,7-dioic lactone (28)

To a solution of the trimethylsilyl ether 24 (73.2 mg, 0.2 mM) in aqueous 80% tert-butyl alcohol at 10° was added potassium carbonate (135 mg, 0.8 mM) dissolved in sodium meta-periodate solution (24 ml, 0.1 M solution, 2.4 mM). The solution was allowed to warm to room temperature and stirred for an additional 14 hours. The excess reagent was destroyed by the addition of ethylene glycol (15 drops) and the stirring continued at room temperature for 3 hours. The solution was concentrated at 20° to remove tert-butyl alcohol and then extracted with chloroform (3 x 5 ml). The aqueous layer was cooled to 5° and then carefully acidified to pH=3 (bromocresol green indicator) with aqueous 1 N sulphuric acid. After saturation of the aqueous solution with sodium chloride and extraction with ethyl acetate (5 x 10 ml), the combined organic layers were dried (Na_2SO_4) and the solvent removed. The remaining residue was purified by column chromatography on silicic acid (2.5 g) using chloroform as solvent and increasing gradually to a 95:5 mixture of chloroform and methanol. The resulting 45 mg of white micro crystals was recrystallized from ether-pentane to give 34 mg (50%) of 28 as white crystals.

PHYSICAL DATA FOR 28

mp: 88-89°

ir ($CHCl_3$): 3200-2200 (bs), 1710 (bs), 1680 (bs)

^1H nmr ($CDCl_3$): δ 1.30 (d, J_d=7.0, 3H), 1.42-2.10 (m, 5H), 2.48 (ddq, J_d=11.0, J_d=7.0, J_q=5.0, 1H), 3.39 (s, 3H), 3.56 (s, 3H), 3.65 (t, J_t=6.0, 2H), 3.96 (d, J_d=1.5, 1H), 4.58 (dd, J_d=9.0, J_d=1.5, 1H), 4.64 (s, 2H), 6.5-7.0 (bs, 1H)

Mass Spectrum: (m/e intensity assignment)
290 (M^+, 0%), 245 (M^+-CO_2H, 0.5%), 201 (M^+-CO_2H-CO_2, 20.2%), 169 (M^+-CO_2H-CO_2-CH_3OH, 16.6%)
CI (melt 60°/PT 145°)
308 ($M^+ + NH_4^+$ (18), 100%)

Elemental Analysis: calcd for $C_{13}H_{22}O_7$: C 53.78, H 7.64, O 38.58
found: C 53.30, H 7.57, O 37.81

Methyl(±)-3S-hydroxy,2S-methoxy-4R-(3,5-dioxahexyl)-6R-methyl heptan-3,7-lactone-1-carboxylate (29)

The lactonic acid (2.9 mg, 0.01 mM) was dissolved in dry methylene chloride (0.1 ml) and treated with excess ethereal diazomethane. After evaporation of solvent and column chromatography on silica gel (0.5 g) using ether as solvent and increasing gradually to ether:ethyl acetate 95:5, 1.5 mg (50%) of methyl ester 29 was obtained as an oil.

PHYSICAL DATA FOR 29

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.30-2.15 (m, 5H), 2.38 (m, J_m=7.0, 1H), 3.38 (s, 3H), 3.52 (s, 3H), 3.63 (t, J_t=6.0, 2H), 3.82 (s, 3H), 3.93 (d, J_d=2.2, 1H), 4.49 (dd, J_d=9.7, J_d=2.2, 1H), 4.62 (s, 2H)

Mass Spectrum: CI (melt 60°/PT 100°)
322 ($M^+ + NH_4^+$, 100%)

Thallium(1) 2-Methyl-2-propanethiolate

2-Methyl-2-propanethiol (1.98 g, 22 mM) was added dropwise over 5 minutes to a solution of Tl(1) ethoxide (5.0 g, 20 mM) in anhydrous benzene (20 ml). After 15 minutes the precipitate was filtered under argon and washed thoroughly with anhydrous pentane (5 x 10 ml) to give 5.6 g (95%) of thallium(1)-2-methyl-2-propanethiolate as bright yellow crystals (mp 170-175°, decomp).

S-tert-Butyl(±)-3S-hydroxy-2S-methoxy-4R -(3,5-dioxahexyl)-6R-methyl heptan-3,7-lactone-1-thiolate (30)

The procedure followed was that reported by Masamune and co-workers.[100]

To a solution of lactonic acid 28 (10.2 mg, 0.035 mM) and triethylamine (3.95 mg, 0.039 mM) in anhydrous benzene (0.35 ml) at 5° was added diethylphosphorochloridate (6.7 mg, 0.039 ml) in anhydrous benzene (0.35 ml). The solution was stirred at 5° for an additional 20 minutes and then at room temperature for 3 hours. The precipitated triethylamine hydrochloride was removed by filtration and washed with dry benzene (2 ml). To the combined filtrate and washings was added thallium(1)-2-methyl-2 propanethiolate (11.35 mg, 0.039 mM). The mixture was stirred at room temperature for 12 hours and the solvent removed. Column chromatography on silica gel (0.5 g) using chloroform as solvent and increasing to a 95:5 mixture of chloroform: methanol gave 6.2 mg (50%) of 30 as an oil.

PHYSICAL DATA FOR 30

^{1}H nmr ($CDCl_3$): δ 1.27 (d, J_d=7.0, 3H), 1.32-2.42 (m, 5H), 1.53 (s, 9H), 2.47 (m, J_m=7.0, 1H), 3.38 (s, 3H), 3.58 (s, 3H), 3.63 (t, J_t=6.0, 2H), 3.74 (d, J_d=2.0, 1H), 4.48 (dd, J_d=10.0, J_d=2.0, 1H), 4.62 (s, 2H)

Mass Spectrum: CI (melt 60°/PT 100°)

380 ($M^+ + NH_4^+$, 100%)

p-Bromophenocyl Ester (31)

The procedure followed was that reported by J. B. Hendrickson.[103]

The lactonic acid 28 (9.4 mg, 0.032 mM) was dissolved in water (0.2 ml) containing a trace amount of phenophthalein indicator and basified with sodium hydroxide (0.096 N), then just acidified to pH=6.5 with aqueous 0.1 N sulphuric acid. To this solution was added p-bromophenacyl bromide (9.0 mg, 0.032 mM) in methanol (0.4 ml) and the reaction stirred at 60° for 6 hours. After cooling to 20° and evaporation of the methanol, the aqueous solution was carefully saturated with sodium chloride and extracted with ethyl acetate (4 x 5 ml), dried (Na_2SO_4) and solvent removed. Column chromatography over silica gel (1 gm), using chloroform as eluent and increasing polarity to chloroform:methanol 98:2, afforded 5.1 mg (35%) of 31 as an oil. Due to the inefficiency of the reaction, a modification is reported.

The lactonic acid 28 (14.5 mg, 0.05 mM) was dissolved in aqueous 80% tert-butyl alcohol containing a trace of phenophthalein at room temperature, followed by dropwise addition of aqueous 0.096 N sodium hydroxide (0.52 ml, 0.05 mM) over 2 minutes, at 5°, with stirring. After stirring at 5° for 15 minutes, the solvent was removed at room temperature on a vacuum pump. The residue was dried by co-evaporation with dry pyridine (1 ml), then dry dioxane-dimethyl-

formamide (1:1, 1 ml) with removal of all solvents at 20° (0.2 mm). The residue was taken up in dry dimethylformamide (0.5 ml) and α-p-dibromoacetophenone (14 mg, 0.05 mM) added in one portion. The stirring was continued at room temperature for 6 hours and the solvent removed on a vacuum pump. The residue was suspended in water (1 ml) and then extracted with chloroform (4 x 1 ml), dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed over silica gel (1.0 g), using chloroform as eluent and increasing polarity to chloroform:methanol 98:2, to afford 23 mg (95%) of 31 as a pale yellow oil.

PHYSICAL DATA FOR 31

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.28-2.10 (m, 5H), 2.5 (m, 1H), 3.36 (s, 3H), 3.60 (s, 3H), 3.62 (bt, J_t=6.0, 2H), 4.15 (d, J_d=2.0, 1H), 4.56 (dd, J_d=10.0, J_d=2.0, 1H), 4.62 (s, 2H), 5.44 (s, 2H), 7.65 (bd, J_d=8.0, 2H), 7.74 (bd, J_d=8.0, 2H)

Hydroxy-p-phenacylbromo Ester (32)

To the methoxy methyl lactonic ester 31 (5.1 mg, 0.01 mM) dissolved in dry carbon tetrachloride (53 μl), was added trimethylsilylbromide (53 μl of a 0.296 M solution in dry carbon tetrachloride, 0.013 mM) and the reaction vigorously stirred for 5 minutes. After adding methanol (2 ml), the solvents were removed under reduced pressure at 20° and co-evaporated with dry benzene (2 x 2 ml). The residue was dissolved in dichloromethane (2 ml), washed with aqueous 5% sodium bicarbonate (2 x 0.5 ml), dried (Na_2SO_4) and the solvent evaporated to give an oil. This oil was chromatographed over silica gel (0.5 g) using chloroform as eluent and increasing polarity to chloroform:methanol 98:2 to afford 4 mg (86%) of 32 as an oil.

PHYSICAL DATA FOR 32

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=8.0, 3H), 1.42-2.84 (m, 7H), 3.60 (s, 3H), 3.78 (t, J_t=6.0, 2H), 4.18 (d, J_d=2.0, 1H), 4.56 (dd, J_d=10.0, J_d=2.0, 1H), 5.42 (s, 2H), 7.60 (bd, J_d=8.0, 2H), 7.78 (bd, J_d=8.0, 2H)

Aldehyde (33)

The procedure followed was that reported by E. J. Corey and co-workers.[104]

To a stirred solution of alcohol 32 (8 mg, 0.018 mM) (dried by benzene azeotrope) in dry methylene chloride (1 ml) at 0-5° was added pyridinium chlorochromate (6 mg, 0.027 mM) and sodium acetate (0.5 mg, 0.006 mM). The mixture was stirred for 2 hours at room temperature and diluted with ethyl acetate:ether 3:97 (1 ml). This solution was directly chromatographed over silica gel (0.8 g), using ether as eluent and changing to ether:ethylacetate 95:5, to afford 7 mg (90%) of 33 as an oil.

PHYSICAL DATA FOR 33

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.10-1.82 (m, 2H), 2.07 (m, 1H), 2.66 (m, 2H), 2.84 (m, 1H), 3.58 (s, 3H), 4.15 (d, J_d=2.5, 1H), 4.57 (dd, J_d=9.5, J_d=2.5, 1H), 5.44 (bs, 2H - due to conformation), 7.66 (bd, 2H), 7.78 (bd, 2H), 9.80 (m, 1H)

Attempt to Form Dimethyl Acetal of 33

To a solution of aldehyde 33 (8 mg, 0.018 mM) in dry tetrahydrofuran (0.15 ml), was added dry methanol (7 μl, 0.18 mM) at 5°, then methyl orthoformate (4 mg, 0.036 mM) and trifluoroacetic acid (0.7 mg, 0.006 mM). The reaction was warmed to room temperature and stirred for 12 hours. The reaction was diluted with ethyl acetate (1.5 ml), then stirred with aqueous saturated sodium chloride (0.5 ml). After separation and re-extraction of the aqueous layer with ethyl acetate (2 x 1 ml), the combined organic layers were dried (Na_2SO_4), containing a small amount of solid sodium bicarbonate, and evaporated to give a tar. Column chromatography over silica gel (0.6 g), using ether as eluent and increasing polarity to ether:ethyl acetate 90:10, gave two compounds, 34, 4 mg (45%) and 35, 2 mg (23%).

PHYSICAL DATA FOR 34

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.12-1.80 (m, ca. 3H), 1.82-2.0 (m, ca. 2H), 2.02-2.22 (m, ca. 1H), 2.55-2.75 (m, ca. 2H), 3.30 (s, 3H), 3.50 (s, 3H), 3.72 (s, 3H), 3.97 (d, J_d=1.5, 1H), 4.55 (dd, J_d=9.0, J_d=1.5, 1H), 5.11 (dd, J_d=4.0, J_d=1.0, 1H), 5.44 (s, 2H), 7.65 (bd, J_d=8.0, J_d=2.0, 2H), 7.79 (bd, J_d=8.0, J_d=2.0, 2H)

PHYSICAL DATA FOR 35

^{1}H nmr ($CDCl_3$): δ 1.21 (d, J_d=7.0, 3H), 1.10-1.82 (m, ca. 3H), 1.82-2.0 (m, ca. 2H), 2.02-2.22 (m, ca. 1H), 2.55-2.75 (m, ca. 2H), 3.40 (s, 3H), 3.55 (s, 3H), 3.99 (d, J_d=4.5, 1H), 4.38 (dd, J_d=6.5, J_d=4.5, 1H), 5.06 (d, J_d=5.0, 1H), 5.42 (s, 2H), 7.60 (s, 3H), 7.65 (bd, J_d=8.0, J_d=2.0, 2H), 7.79 (bd, J_d=8.0, J_d=2.0, 2H)

The possible structures for 34 and 35 arise from similarity with the ^{1}H nmr spectrum of degradation products 36 and 37.

tert-Butylthioacetate (38)

The procedure followed was that reported by Rylander and Tarbell.[113]

Freshly distilled acetyl chloride (10 ml, 11.0 g, 0.14 M) was slowly added to an ice cooled solution of dry pyridine (14 ml, 14.0 g, 0.14 M) in dry chloroform (40 ml). After the addition was complete, 2-methyl-2-propanethiol (14 ml, 11 g, 0.125 M) was added over 30 minutes and the reaction stirred an additional hour at 5°, then at room temperature for 14 hours. The reaction mixture was then cooled to 5°, and ice water (ca. 30 ml) was added. After separation, the organic layer was washed with cold water (20 ml), cold aqueous 1.5 N hydrochloric acid (2 x 25 ml), cold 10% aqueous sodium bicarbonate (2 x 25 ml) and finally cold water (20 ml). After drying (K_2CO_3 / Drierite mixture), the solvent was removed and the residue was distilled under atmospheric pressure using a 10 cm Vigreux column to give 6.8 g (42%) of 38 as a colorless liquid (bp 130-133°, 701 mm).

PHYSICAL DATA FOR 38

^{1}H nmr ($CDCl_3$): δ 1.42 (s, 9H), 2.20 (s, 3H)

Preparation of Half Ester (39)

The procedure followed was that reported by D. W. Brooks.[101]

A hexane solution of n-butyllithium (16.2 ml, 1.6 M, 0.026 M) was added to a solution of diisopropylamine (3.7 ml, 0.026 M) in anhydrous tetrahydrofuran (50 ml) at -40°. The solution was stirred for 15 minutes, then cooled to -78°, and S-tert-butylthioate 38 (6.3 g, 0.024 M) was added dropwise over 10 minutes. After stirring for 30 minutes at this temperature, an excess of dry ice pellets (11 g, 0.25 M) was added. The mixture was allowed to warm to room temperature and the solvent was evaporated under reduced pressure. The residue was suspended in cold (5°) water (25 ml) and acidified by dropwise addition of cold concentrated hydrochloric acid to pH=2. The aqueous mixture was extracted with ether (2 x 25 ml) and the ether layer extracted with aqueous saturated sodium bicarbonate (2 x 15 ml). The aqueous extract was then cooled to 0-5° and carefully acidified to pH=3 by dropwise addition of cold 6 N hydrochloric acid with constant stirring. The aqueous phase was extracted with ether (2 x 20 ml) and the ether extract washed with aqueous saturated sodium chloride, dried (Na_2SO_4) and the solvent removed to give the half ester in 70% yield.

PHYSICAL DATA FOR 39

^{1}H nmr ($CDCl_3$): δ 1.46 (s, 9H), 3.51 (s, 2H), 10.95 (s, 1H)

Preparation of Magnesium Reagent (40)

The procedure followed was that reported by D. W. Brooks.[101]

To a solution of the half ester 39 (10 mM) in anhydrous tetrahydrofuran (25 ml) was added freshly prepared magnesium ethoxide (5 mM). The mixture was stirred for 1 hour during which time a nearly homogeneous solution formed. The mixture was filtered through a pad of Celite and the filtrate was evaporated to give a white solid residue. After pumping under vacuum (0.1 mM, 5 hours), a white amorphous solid was obtained which was ready for use.

PHYSICAL DATA FOR 40

ir ($CDCl_3$): 1680 (s), 1630 (s)

^1H nmr ($CDCl_3$): δ 1.45 (s), 1.48 (s), (ca. 2:1, 9H), 3.32-3.72 (bm, 2H)

S-tert-Butyl-(+)-5S-hydroxy, 3-keto-4S-methoxy-6R (3,5-dioxahexyl)-8R-methyl-heptan-3,7-lactone-1-thiolate (42)

The procedure followed was that reported by D. W. Brooks.[101]

To a solution of lactonic acid 28 (14.5 mg, 0.05 mM) (dried by benzene azeotrope) in dry tetrahydrofuran (0.5 ml), was added carbonyldiimidazole (9 mg, 0.055 mM) at 0°. The mixture was stirred at this temperature for 6 hours. The magnesium salt 40 (15 mg, 0.055 mM) was added in one portion and the solution stirred at room temperature for 12 hours. After the solvent was removed, the residue was diluted with ether (2 ml), extracted with aqueous 40% ammonium sulfate and the aqueous layer extracted with ether (2 ml). The combined ethereal solutions were washed with aqueous 10% sodium bicarbonate (1 ml), aqueous saturated sodium chloride (1 ml) and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed over silica gel (1.0 g) using a chloroform as eluent and increasing polarity to a 97:3 mixture of chloroform:methanol to give 19 mg (94%) of 42 as a white solid.

PHYSICAL DATA FOR 42

mp: 65-66°

^{1}H nmr ($CDCl_3$): δ 1.27 (d, J_d=7.0, 2H), 1.30-2.82 (m, 5H), 1.49 (s, 9H), 3.38 (s, 3H), 3.54 (s, 3H), 3.63 (t, J_t=6.0, 2H), 3.64 (d, J_d=15.5, 1H), 3.77 (d, J_d=1.8, 1H), 4.09 (d, J_d=15.5, 1H), 4.42 (dd, J_d=10.0, J_d=1.8, 1H), 4.63 (s, 2H)

Mass Spectrum: CI (melt 65°/PT 120°)
422 ($M^+ + NH_4^+$ (18), 100%)

Elemental Analysis: calcd for $C_{19}H_{32}O_7S$: C 56.42, H 7.97
found: C 56.38, H 7.95

PHYSICAL DATA FOR 43

^{1}H nmr ($CDCl_3$): δ 1.27 (d, J_d=7.0, 2H), 1.30-2.82 (m, 5H), 1.53 (s, 9H), 3.38 (s, 3H), 3.46 (s, 3H), 3.62 (t, J_t=6.0, 2H), 3.77 (dd, J_d=1.8, J_d=1.0, 1H), 4.37 (dd, J_d=9.0, J_d=1.8, 1H), 5.70 (d, J_d=1.0, 1H), 12.85 (s, 1H)

Imidazolide (44)

To a solution of 1, 1'-carbonyldiimidazole (0.76 g, 4.7 mM) in dry tetrahydrofuran (8 ml) was added isobutyric acid (0.4 ml, 0.38 g, 4.26 mM). After stirring for 4 hours at room temperature, this solution was used directly in the subsequent reaction without isolation of the imidazolide.

β-Ketothiolester (45)

To a solution of the magnesium salt 40 (1.65 g, 4.4 mM) in dry tetrahydrofuran was added the imidazolide solution 44 and the mixture refluxed for 14 hours. After this time, the mixture was allowed to cool to room temperature and the solvent removed. The residue was diluted with cold ether (30 ml) and then with cold aqueous 0.2 N hydrochloric acid (25 ml). After separation, the aqueous layer was extracted with ether (20 ml) and the combined organic layers washed successively with cold saturated aqueous sodium bicarbonate (20 ml) and saturated aqueous sodium chloride. The ether layer was then dried (Na_2SO_4) and the solvent removed to give a yellow oil which after distillation under reduced pressure resulted in a 7:3 mixture of 45 and 46 0.61 g (71%) as a colorless oil.

PHYSICAL DATA FOR 45

^{1}H nmr ($CDCl_3$): δ 1.13 (d, J_d=7.0, 4.2H), 1.49 (s, 6.3H), 2.74 (sept, J_{sept}=7.0, 0.7H), 3.62 (s, 1.4H)

PHYSICAL DATA FOR 46

^{1}H nmr ($CDCl_3$): δ 1.15 (d, J_d=7.0, 1.8H), 1.52 (s, 2.7H), 2.34 (sept, J_{sept}=7.0, 0.3H), 5.32 (s, 0.3H), 12.95 (s, 0.3H)

Attempt to Synthesize (47)

The β-ketothiolester mixture 45 and 46 (28 mg, 1.2 mM) was dissolved in ethanol (2 ml) and hydrogenated with $PtO_2.H_2O$ (5 mg, 0.002 mM). The reaction was followed by vpc and after 1 hour no change was observed. Another 10 mg of catalyst was added and the mixture hydrogenated a further 14 hours with no change observable other than the slow formation of ethyl ester 48 as seen by ^1H nmr.

β-Hydroxythiolester (47)

To a solution of β-ketothiolester mixture 45 and 46 in dry methanol (1 ml) at -20° was added sodium borohydride (4.7 mg, 0.125 mM) and the mixture stirred for 3 hours at this temperature. The mixture was then diluted with 40% aqueous ammonium sulphate (0.5 ml) and the reaction stirred at this temperature for 5 minutes before removing the methanol. The residue was diluted with ether (2 ml) and water (1 ml). After separation, the aqueous layer was washed with ether (2 x 2 ml) and the combined organic layers dried (Na_2SO_4) and the solvent removed to give 49 mg (97%) of 47 as a colorless liquid which showed only one peak by vpc. This material was used directly in the subsequent transformation without further purification.

β-Acetoxythiolester (49)

To a solution of β-hydroxythiolester 47 (40 mg, 0.2 mM) in dry pyridine (1 ml) was added acetic anhydride (0.4 ml) and the mixture stirred at room temperature for 16 hours. The reaction was then cooled to 5° and diluted with 20% aqueous ammonium sulphate (3 ml) and then extracted with a 1:1 mixture of benzene and pentane (3 x 3 ml). The combined organic layers were then washed with 10% aqueous sodium bicarbonate (3 ml), saturated aqueous sodium chloride (3 ml), dried (Na_2SO_4) and the solvent removed to give a pale yellow liquid. This residue was chromatographed over silica gel (2.5 g) using a 19:1 mixture of benzene and ether to give 34 mg (70%) of 49 as a colorless liquid.

PHYSICAL DATA FOR 49

^{1}H nmr ($CDCl_3$): δ 1.90 (d, J_d=7.0, 6H), 1.44 (s, 9H), 1.88 (m, 1H), 2.03 (s, 3H), 2.63 (m, 2H), 5.11 (dt, J_d=6.5, J_t=5.8, 1H)

Stability of 49 Towards Base

A mixture of the acetoxythiolester 49 (10 mg, 0.04 mM) in tert-butyl alcohol (0.5 ml) was added to an aqueous 0.198 N potassium hydroxide solution at 5° and stirring was continued for 14 hours at this temperature. After this time, the mixture was diluted with ether (1 ml) and acidified to pH ca. 4 with aqueous 0.1 N hydrochloric acid. After separation, the aqueous layer was washed with ether (3 x 1 ml), the combined organic layers washed with saturated aqueous sodium chloride (1 ml), dried (Na_2SO_4) and the solvent removed to give a pale yellow oil. This residue was chromatographed over silica gel (0.5 g) using pentane as eluent and slowly changing to a 19:1 mixture of pentane and ether to give 8 mg (90%) of 50 as a colorless oil.

PHYSICAL DATA FOR 50

^{1}H nmr ($CDCl_3$): δ 1.06 (d, J_d=7.0, 6H), 1.49 (s, 9H), 2.30 (m, 1H), 5.93 (dd, J_d=16.0, J_d=1.5, 1H), 6.76 (dd, J_d=16.0, J_d=6.5, 1H)

A mixture of the β-acetoxythiolester 49 (2.1 mg, 0.01 mM) and imidazole (3.5 g, 0.05 mM) in dry DMF (0.1 ml) was stirred at 60° for 20 hours. The vpc showed most of the product was the elimination product 50.

Stability of 49 to Trimethylbromosilane

To a stirred solution of β-acetoxythiolester 49 (10 mg, 0.04 mM) in dry carbon tetrachloride (178 μl) was added the trimethylsilylbromide solution (0.296 M, 178 μl, 0.052 mM) and the mixture stirred at room temperature for 10 minutes. The mixture was then diluted with methanol (1 ml) and the solvents removed. The residue was taken up in chloroform (1 ml) and passed through a short column of a 1:1 mixture of sodium sulphate and potassium carbonate. Evaporation of solvent gave 9.9 mg of oil which was identical by ^{1}H nmr to the starting material.

S-tert-Butyl-(±)-5S-hydroxy-3S-hydroxy-4S-methoxy-6R(3,5-dioxahexyl)-8R-methyl-heptan-5,9-lactone-1-thiolate (51)

The details for preparation of alcohol 51 appear in the research report of Dr. H. Yamamoto.[106]

PHYSICAL DATA FOR 51

^{1}H nmr ($CDCl_3$): δ 1.27 (d, J_d=7.0, 3H), 1.30-1.42 (m, 3H), 1.49 (s, 9H), 1.70-2.52 (m, 4H), 2.71-3.05 (m, 2H), 3.39 (s, 3H), 3.45 (dd, J_d=4.5, J_d=2.0, 1H), 3.58 (s, 3H), 3.63 (bt, J_t=6.0, 2H), 3.60-3.82 (m, 1H), 4.32 (dd, J_d=9.0, J_d=2.0, 1H), 4.63 (s, 2H)

Mass Spectrum: CI (melt 65°/PT 140°)
424 ($M^+ + NH_4^+$ (18), 100%)

β-Acetoxythiolester (52)

To a solution of β-hydroxythiolester 51 (4.0 mg, 0.0098 mM) in dry pyridine (0.3 ml) was added acetic anhydride (0.15 ml, excess) at 0°. The mixture was allowed to warm to room temperature and stirred for 12 hours. Evaporation of volatile material on a vacuum pump gave a pale yellow residue which was dissolved in benzene:pentane 1:1 (2 ml). The organic solution was washed with cold aqueous 10% sodium bicarbonate (2 x 0.5 ml) and dried (Na_2SO_4). Evaporation of solvent and column chromatography over silica gel (0.5 g) using chloroform as eluent and increasing polarity to chloroform:methanol 95:5, gave 2.3 mg (50%) of 52 as an oil.

PHYSICAL DATA FOR 52

^{1}H nmr ($CDCl_3$): δ 1.26 (d, J_d=7.0, 3H), 1.46 (s, 9H), 2.10 (s, 3H), 1.88-2.63 (m, 6H), 2.96 (dd, J_d=16.0, J_d=6.5, 1H), 2.99 (dd, J_d=16.0, J_d=4.5, 1H), 3.38 (s, 3H), 3.55 (s, 3H), 3.60 (dd, J_d=6.0, J_d=1.5, 1H), 3.62 (bt, J_t=5.5, 2H), 4.30 (dd, J_d=9.0, J_d=1.5, 1H), 4.63 (s, 2H)

Mass Spectrum: CI (melt 65°/PT 105°)
466 ($M^+ + NH_4^+$ (18), 100%)

Dr. H. Yamamoto has shown that ring opening of compounds 51 and 52 did not lead to the desired compounds. Some complications arose from the presence of methoxy methyl protecting group in this molecule.

Alcohol (54)

To a stirred solution of β-acetoxythiolester 52 (20 mg, 0.005 mM) in dry carbon tetrachloride (300 μl) was added trimethylsilylbromide (0.296 M) in carbon tetrachloride (220 μl, 0.007 mM) and the reaction stirred at room temperature for 10 minutes. Anhydrous methanol (2 ml) was then added to the rapidly stirred solution; the solvent was removed and finally the remaining volatile side products were removed in vacuo. The residue was diluted with benzene and the solvent and volatile materials were again removed. The remaining yellow oil was dissolved in chloroform (1 ml) and passed through a short column of anhydrous sodium sulphate containing potassium carbonate. The remaining residue was chromatographed over silica gel (0.8 g) into ca. 0.5 ml fractions using a 3:17 mixture of ethyl acetate and ether to give 11.6 mg (62%) of 54 as a colorless oil. The starting material 52 (2.5 mg) was also recovered. All coupling constants were confirmed by decoupling (irradiation at δ 2.1, 3.0, 3.6 and 5.45).

PHYSICAL DATA FOR 54

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.37 (bq, J_q=12.5, 1H), 1.46 (s, 9H), 1.70 (bs, 1H), 1.6-1.8 (m, 2H), 2.03 (ddd, J_d=12.5, J_d=5.0, J_d=4.0, 1H), 2.09 (s, 3H), 2.27 (dtt, J_d=12.5, J_t=9.0, J_t=4.0, 1H), 2.50 (dqd,

J_d=12.5, J_q=7.0, J_d=5.0, 1H), 2.93 (dd, J_d=16.0, J_d=7.0, 1H), 3.04 (dd, J_d=16.0, J_d=4.0, 1H), 3.56 (s, 3H), 3.65 (dd, J_d=6.3, J_d=1.3, 1H), 3.78 (bt, J_t=5.8, 2H), 4.35 (dd, J_d=9.0, J_d=1.3, 1H), 5.56 (ddd, J_d=7.0, J_d=6.3, J_d=4.0, 1H)

Mass Spectrum: CI (melt 65°/PT 135°)

422 ($M^+ + NH_4^+$ (18), 100%)

Preparation of Pyridinium Dichromate

The procedure followed was that reported by E. J. Corey and G. Schmidt.[108]

Chromium trioxide (50 g, 0.5 M) was dissolved in water (50 ml) and the solution cooled in an ice water bath. Pyridine (40.3 ml, 39.57 g, 0.5 M) was added to the stirred solution at such a rate that the temperature did not rise above 30°. A thick orange precipitate formed after the addition of ca. 20 ml of pyridine. After the addition was complete, acetone (200 ml) was added, the precipitate broken up and the solution cooled at -20° for 2 hours. The solid was collected by filtration, washed with cold acetone and dried in vacuo to give 68.6 g (73%) of pyridinium dichromate as a bright orange solid (mp 143-145°).

Aldehyde (55)

To a stirred solution of the alcohol 54 (11.6 mg, 0.029 mM) in dry methylene chloride (0.3 ml) was added pyridinium dichromate (10 mg, 0.024 mM) and the mixture was stirred at room temperature for 6 hours. After this time, another portion of pyridinium dichromate (10 mg) was added and the stirring continued for 12 hours. The mixture was directly chromatographed over silica gel (0.5 g) into ca. 0.5 ml fractions using chloroform as eluent and gradually changing to a 19:1 mixture of chloroform and methanol, to give 7 mg (65%) of 55 as a colorless oil.

PHYSICAL DATA FOR 55

^{1}H nmr ($CDCl_3$): δ 1.24 (d, J_d=7.0, 3H), 1.40 (m, 1H), 1.46 (s, 9H), 2.01 (ddd, J_d=13.0, J_d=5.5, J_d=4.0, 1H), 2.09 (s, 3H), 2.48-2.80 (m, 5H), 2.89 (dd, J_d=16.0, J_d=7.0, 1H), 3.01 (dd, J_d=16.0, J_d=4.0, 1H), 3.54 (s, 3H), 3.62 (dd, J_d=6.0, J_d=1.5, 1H), 4.36 (dd, J_d=9.0, J_d=1.5, 1H), 5.54 (ddd, J_d=7.0, J_d=6.0, J_d=4.0, 1H), 9.85 (bs, 1H)

Mass Spectrum: CI (melt 65°/PT 145°)
420 ($M^+ + NH_4^+$ (18), 100%)

Hemiacetals (56) and (57)

The aldehyde 55 (7 mg, 0.018 mM) was treated with a 1:1 mixture of water and acetonitrile containing 1.5% trifluoroacetic acid (0.5 ml) at 5° and then allowed to stir at room temperature for 1.5 hours. After this time, the mixture was cooled to 5°, diluted with ethyl acetate (2 ml) and saturated aqueous sodium chloride (1 ml), and rapidly stirred for ca. 5 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 2 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed to give 5 mg (70%) of 56 and 57 as a colorless tar which was used directly in the subsequent transformation without further purification.

PHYSICAL DATA FOR 56 AND 57

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.47 (s, 9H), 1.10-3.0 (m, 9H), 2.07 (s, 3H), 3.50 (m, 1H), 3.58 (s, 3H), 4.15 (dd, J_d=7.0, J_d=1.0, 1H), 5.37 (m, 1H), 5.55 (m, 1H), 7.10 (bs, ca. 1H)

Acetals (58) and (59)

The crude hemiacetal mixture of 58 and 59 (5 mg, 0.014 mM) was treated with a freshly prepared stock solution (0.5 ml) made by dissolving trifluoroacetic acid (0.07 ml), methyl orthoformate (0.24 ml) and dry methanol (3 ml) in dry tetrahydrofuran (7 ml) and the stirring continued at room temperature for 24 hours. The mixture was then diluted with ethyl acetate (2 ml) and saturated aqueous sodium chloride (1 ml) followed by stirring for ca. 1 minute and separating the layers. The aqueous layer was extracted with ethyl acetate (3 x 1 ml), the combined organic layers dried (Na_2SO_4) and the solvent removed to yield 8 mg of tar. This tar was chromatographed over silica gel (0.15 g) using chloroform as eluent and slowly increasing polarity to a 99:1 mixture of chloroform and methanol, to give 2.7 mg (60%) of 58 and 59 as a colorless tar and 1.4 mg of starting material contaminated with other impurities.

PHYSICAL DATA FOR 58 AND 59

^{1}H nmr ($CDCl_3$): δ 1.25 (d, J_d=7.0, 3H), 1.47 (s, 9H), 1.40-1.92 (m, 4H), 2.07 (s, 3H), 2.50 (m, 2H), 2.94 (dd, J_d=16.0, J_d=8.5, 1H), 3.00 (dd, J_d=16.0, J_d=4.5, 1H), 3.35 (s, 3H), 3.45 (m, 1H), 3.51 (s, 3H), 4.18 (dd, J_d=7.2, J_d=3.0, 1H), 5.05 (dd, J_d=5.5, J_d=1.5, 1H), 5.55 (dt, J_d=8.5, J_t=4.5, 1H)

Acetal (60)

This sample was obtained by Dr. S. Mori[86] from degradation of the natural product. The ^1H nmr of 60 fits very closely with that of 58 and 59, therefore stereochemistry of the asymetric centers in the synthetic product seems to be correct.

PHYSICAL DATA FOR 60

^1H nmr ($CDCl_3$): δ 1.24 (d, J_d=7.0, 3H), 1.32 (ddd, J_d=13.0, J_d=11.0, J_d=4.3, 1H), 1.84 (ddd, J_d=13.0, J_d=10.0, J_d=4.0, 1H), 1.88 (ddd, J_d=13.0, J_d=8.0, J_d=5.5, 1H), 1.95 (ddd, J_d=13.0, J_d=8.5, J_d=1.5, 1H), 2.06 (s, 3H), 2.46 (m, 2H), 2.80 (dd, J_d=15.5, J_d=8.5, 1H), 2.88 (dd, J_d=15.5, J_d=4.0, 1H), 3.35 (s, 3H), 3.42 (dd, J_d=4.0, J_d=3.0, 1H), 3.50 (s, 3H), 3.78 (s, 3H), 4.17 (dd, J_d=7.2, J_d=3.0, 1H), 5.03 (dd, J_d=5.5, J_d=2.0, 1H), 5.55 (ddd, J_d=8.5, J_d=4.2, J_d=4.0, 1H), 6.6 (bs, 1H)

Mass Spectrum: CI (melt 65°/PT 160°)

394 ($M^+ + NH_4^+$ (18), 100%)

Imidazolide (63)

1, 1'-carbonyldiimidazole (295 mg, 1.82 mM) was added to a solution of 2-ethylhexanoic acid (259 mg, 1.80 mM) in dry methylene chloride (3 ml) and a rapid evolution of gas occurred. After 3 hours, the solvent was removed and the residue triturated with pentane (2 x 5 ml) and filtered. The imidazolide (350 mg, 98%) was obtained from the pentane extract as a colorless oil.

Salt-free Triphenylmethylene Phosphorane

The reaction was carried out according to the procedure reported by Schlosser and Christhann.[110]

Anhydrous ammonia (ca. 80 ml) was condensed into a flask at -78° containing a few small pieces of sodium metal. Approximately 60 ml of ammonia was then distilled from the intense blue solution into another flask at -78°. To this solution was added sodium metal (200 mg, 8.3 mg-atom) and a trace amount of iron III chloride. Triphenylmethylphosphonium bromide (2.46 g, 6.90 mM) was then added to the solution and the reaction mixture stirred at -78° for 10 minutes before the ammonia was allowed to evaporate. The solid green residue was then dried at room temperature under reduced pressure (0.1 mm), refluxed in anhydrous benzene (40 ml) for 10 minutes, cooled to room temperature and finally filtered in an argon filled glove bag, to give a bright yellow solution of the ylid. The concentration was found to be 0.144 M as determined by titration of the phosphorane with a standard solution of benzoic acid in benzene. The solution was stored under argon at -15°.

Phosphorane (64)

The procedure followed was that reported by Staab, Sommer and Bestmann.[111]

A salt-free solution of the methylenetriphenyl phosphorane (270 μl, 0.039 mM) was added to a solution of the imidazolide 63 (5.5 mg, 0.03 mM) in dry benzene (100 μl). After stirring at room temperature for 3 hours, the mixture was diluted with ether (4 ml), washed with water (1 ml), saturated aqueous sodium chloride (1 ml) and dried ($MgSO_4$). Evaporation of solvent gave 9.9 mg (89%) of 64 as a colorless oil.

PHYSICAL DATA FOR 64

^1H nmr ($CDCl_3$): δ 0.8-1.1 (m, 6H), 1.2-1.8 (m, 8H), 2.15 (bs, 1H), 3.35-3.8 (bs, 1H), 7.2-7.8 (m, 15H)

Imidazolide (65)

To the methyl ester 60 (3.4 mg, 0.009 mM) in dry methylene chloride (200 μl) cooled to 10° was added carbonyldiimidazole (3.2 mg, 0.018 mM) and the reaction stirred at this temperature for 8 hours. The solvent was then removed and the residue triturated with dry pentane (3 x 1 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed to give 2.5 mg (63%) of 65 as a colorless oil. The extraction residue was dissolved in methylene chloride and evaporated to give 6 mg of white solid. The acid 60 could be separated from imidazole by acidification to pH=3 with aqueous 0.01 N hydrochloric acid 5° against bromocresol green indicator, extraction into ethyl acetate and column chromatography over silica gel.

PHYSICAL DATA FOR 65

^{1}H nmr ($CDCl_3$): δ 1.39 (d, J_d=7.0, 3H), 1.51 (m, 1H), 1.83-1.87 (m, 2H), 2.09 (s, 3H), 2.16 (ddd, J_d=14.0, J_d=9.5, J_d=3.5, 1H), 2.39 (ddt, J_d=10.5, J_d=7.5, J_t=3.5, 1H), 2.81 (dd, J_d=16.5, J_d=8.5, 1H), 2.92 (dd, J_d=16.5, J_d=4.0, 1H), 3.12 (dqd, J_d=9.5, J_q=7.0, J_d=4.5, 1H), 3.22 (s, 3H), 3.48 (m, 1H), 3.49 (s, 3H), 3.70 (s, 3H), 4.20 (dd, J_d=7.5, J_d=2.2, 1H), 5.02 (bt, J_t=3.2, 1H), 5.56 (ddd, J_d=8.5, J_d=4.5, J_d=4.0, 1H), 7.12 (bs, 1H), 7.50 (bs, 1H), 8.22 (bs, 1H)

Phosphorane (66)

To the imidazolide 65 (3.3 mg, 0.0077 mM) in dry benzene (300 μl) cooled to 10° was added the salt-free benzene solution of triphenylmethylene phosphorane (80 μl, 0.011 mM) and the reaction stirred at this temperature for 6 hours. The reaction mixture was then diluted with ether (2 ml) and saturated aqueous sodium chloride (1 ml) and stirred for 5 minutes. After separation, the aqueous layer was extracted with ether (2 x 2 ml), the combined organic layers were dried (Na_2SO_4) and solvent removed, to give 8 mg of 66.

PHYSICAL DATA FOR 66

^{1}H nmr ($CDCl_3$): δ 1.3 (d, 3H), 1.88 (m, 2H), 2.03 (s, 3H), 2.2-2.3 (m, 1H), 2.8-3.0 (m, 2H), 3.31 (s, 3H), 3.42 (s, 3H), 3.44 (m, 1H), 3.64 (s, 3H), 4.19 (dd, J_d=7.5, J_d=3.0, 1H), 5.01 (bt, J_t=4.5, 1H), 5.52 (m, 1H), 7.74-7.78 (m, 15H)

Ethyl β-Hydroxybutyrate (68)

The procedure followed was that reported by House.[114] Ethyl acetoacetate (13 g, 0.1 M) was dissolved in methanol (100 ml) and the solution cooled to 0°. Sodium borohydride (1.9 g, 0.05 M) was added over ca. 20 minutes to the rapidly stirred solution after which the solution was allowed to stir at this temperature for an additional 4 hours. The solution was then acidified to pH 4.5 with aqueous 2 N hydrochloric acid and concentrated to a volume of ca. 40 ml. The aqueous residue was extracted with ether (3 x 40 ml), dried (Na_2SO_4) and the solvent removed. The crude ester was purified by distillation (bp 70°/15 mm) to give 8.46 g (65%) of 68 as a colorless oil.

PHYSICAL DATA FOR 68

^{1}H nmr ($CDCl_3$): δ 1.21 (d, 3H), 1.30 (t, 3H), 2.48 (d, 2H), 3.32 (bs, 1H), 4.22 (m, 3H)

β-Hydroxybutyric Acid (69)

The procedure followed was that reported by McCann and Greville.[115]

Ethyl β-hydroxybutyrate 68 (8.46 g, 0.065 M) was suspended in water (20 ml) and aqueous 4 N sodium hydroxide (16.25 ml) was added dropwise to the stirred solution. After the addition was complete, stirring was continued for 14 hours. The solution was then acidified to pH=2 with an aqueous 5 N sulphuric acid. The use of continuous extraction with ether over 14 hours, followed by drying (Na_2SO_4) of the organic layer and removal of solvent, yielded 5.01 g (74%) of 69 as a syrupy residue.

Resolution of β-Hydroxybutyric Acid (70)

The procedure followed was that reported by McCann and Greville.[115]

Quinine monohydrate was dried to constant weight over concentrated sulphuric acid in vacuo. To a solution of β-hydroxybutyric acid 69 (5.01 g, 0.048 M) in acetone (40 ml) was added quinine and the mixture was refluxed until the solid dissolved. The solution was cooled to 0° and allowed to stand at this temperature for 24 hours. The precipitated L-(+)-quinine salt was filtered off and the filtrate concentrated to give a solid residue. The solid was triturated with ether and then with petroleum ether. The crude salt was recrystallized from warm water (below 70°) using ca. 2 ml of water per gram of solid. The solution was filtered to remove insoluable impurities and allowed to stand at 0° for three days. The recrystallization procedure was repeated twice more to give 5.98 g (28%) of the D-(-)-salt mp 60-65° (literature mp 60-70° with 4.5 molecules of water of crystallization).

The D-(-)-quinine salt (5.98 g, 13.4 mM) was suspended in water (15 ml) and an aqueous sulphuric acid solution (4.8 ml), prepared by mixing 3.2 ml of water and 1.6 ml of concentrated acid, was added dropwise to the stirred mixture. A precipitate of quinine sulfate appeared, but

re-dissolved as the acidification proceeded. The aqueous solution was continuously extracted with ether for 12 hours, the organic layer dried ($MgSO_4$) and the solvent removed, to give 0.96 g (69% based on the D-(-)-quinine salt) of D-(-)-β-hydroxybutyric acid 70.

The optical rotation of a solution of the resolved acid (0.3319 g, 3.19 mM) in water (6 ml) was found to be $[\alpha]_D^{20}$=-25.0 (literature $[\alpha]_D$=-25.8).[115] This acid was directly converted to its methyl ester.

R-Methyl-β-hydroxybutyrate (71)

A solution of D(-)-β-hydroxybutyric acid 70 (0.33 g, 3.1 mM) was dissolved in ether (5 ml) and treated with excess ethereal diazomethane. The solvent was removed and the residue dissolved in ether (10 ml), dried ($MgSO_4$) and the solvent removed leaving 0.368 g (99%) of 71 as a yellow oil. This ester was used directly in the next step without further purification.

PHYSICAL DATA FOR 71

^{1}H nmr ($CDCl_3$): δ 1.2 (d, 3H), 2.45 (d, 2H), 3.1 (bs, 1H), 3.7 (s, 3H), 4.2 (m, 1H).

R-Methyl β-(2-Tetrahydropyranyl)oxybutyrate (72)

Dihydropyran was dried over Na_2CO_3, distilled, and distilled once more from sodium.

R-Methyl β-hydroxybutyrate 71 (0.368 g, 3.12 mM) was dissovled in chloroform (3 ml). After cooling to -70°, dihydropyran (1 ml) and trifluoroacetic acid were added to the stirred solution and then the solution was allowed to warm to room temperature. The mixture was then stirred at room temperature for 2 hours, diluted to 40 ml with chloroform, washed with aqueous saturated sodium carbonate (3 x 15 ml) and aqueous saturated sodium chloride (1 x 15 ml), and dried (Na_2SO_4). The solvent was removed and the residue chromatographed over silica gel (20 g) using pentane as eluent and gradually changing to pentane and ether 1:1, to give 0.61 g (96%) of 72 as a colorless oil.

PHYSICAL DATA FOR 72

^1H nmr ($CDCl_3$): δ 1.20 (m, 3H), 1.54 (m, 6H), 2.50 (d, 2H), 3.45-3.90 (m, 2H), 3.50 (s, 3H), 4.30 (m, 1H), 4.72 (m, 1H)

3R-(2-Tetrahydropyranyl)oxybutanol (73)

The tetrahydropyranyl ether 72 (0.6 g, 2.9 mM) was dissolved in anhydrous ether (5 ml) and added dropwise over 10 minutes to a stirred solution of lithium aluminum hydride (0.22 g, 5.8 mM) in anhydrous ether (5 ml). After 30 minutes, the reaction was quenched with saturated aqueous sodium sulfate and the layers separated. The aqueous layer was washed with ether (2 x 10 ml), the combined organic extracts dried (Na_2SO_4) and the solvent removed to give, presumably, 73 as an oil. Due to the ease of migration of the tetrahydropyranyl group to the primary alcohol,[109] this compound was immediately oxidized to the aldehyde.

PHYSICAL DATA FOR 73

^{1}H nmr ($CDCl_3$): δ 1.19 (m, 3H), 2.38-2.94 (m, 8H), 2.35 (bs, 1H), 3.32-4.14 (m, 5H), 4.56 (m, 1H)

glpc (UC W98): 160°

3R-(2-Tetrahydropyranyl)oxybutanal (74)

The alcohol 73 (0.35 g, 2.0 mM) and pyridinium dichromate (0.75 g, 4.0 mM) were dissolved in dichloromethane (12 ml) and stirred for 24 hours at room temperature. After this time, the suspension was diluted with ether (20 ml) and filtered through magnesium sulfate. The solvent was removed and the residue purified by column chromatography over silica gel (5 g) using pentane as eluent and gradually changing to pentane and ether 1:1 to give 0.3 g (85%) of 74 as a colorless oil.[116]

PHYSICAL DATA FOR 74

bp: 109-110°, 12 mm

^{1}H nmr ($CDCl_3$): δ 1.19 (d, J_d=6.0, 3H), 1.55 (m, 6H), 2.52 (m, 2H), 3.5-3.9 (m, 2H), 4.25 (sextet, J_{sextet}=6.5, 1H), 4.72 (m, 1H), 9.85 (t, J_t=2.5, 1H)

glpc (UC W98): 150°

Formylmethyltriphenylphosphorane (75)

The procedure followed was that reported by Triplett et al.[117]

To a stirred suspension of methyltriphenylphosphonium bromide (10.7 g, 0.029 M) in ether (100 ml) was added ethereal 1.16 N butyllithium (25 ml, 0.03 M) and the solution was stirred at room temperature for 30 minutes. After this time, the ethereal solution was slowly added to a stirred solution of ethyl formate (2.7 g, 0.033 M) in ether (50 ml). After an additional 30 minutes of stirring, the solution was extracted with aqueous 5% hydrochloric acid (2 x 100 ml) and the combined extracts made alkaline (pH=10) with aqueous 0.5 N sodium hydroxide. The aqueous solution was extracted with benzene (3 x 200 ml) and the solvent removed to give 6.1 g of 75. This solid was quickly recrystallized from acetone to give 5 g (70%) of solid.

PHYSICAL DATA FOR 75

mp:	186-187° (decomp)
Elemental Analysis:	calcd for $C_{20}H_{17}OP$: C 78.91, H 5.82
	found: C 78.89, H 5.76

5R-(2-Tetrahydropyranyl)oxy-2-hexenal (76)

A solution of aldehyde 74 (0.2 g, 1.16 mM) and phosphorane 75 (0.35 g, 1.16 mM) in benzene (10 ml) was refluxed for 17 hours. After this time, the solvent was removed and the residue chromatographed over silica gel (4 g) using pentane and gradually changing to pentane and ether 1:1 to give 0.11 g (50%) of aldehyde 76 as a colorless oil.

PHYSICAL DATA FOR 76

^{1}H nmr ($CDCl_3$): δ1.22 (m, 3H), 1.4-1.9 (m, 6H), 2.53 (m, 2H), 3.45 (m, 1H), 3.85 (m, 1H), 4.08 (m, 1H), 4.68 (m, 1H), 6.14 (m, 1H), 6.88 (m, 1H), 9.52 (d, J_d=8.0, 1H)

glpc (UC W98): 190°

5R-Hydroxy-2-hexenal (77)

The aldehyde 76 (30 mg, 0.15 mM) was dissolved in a solution of acetonitrile and methanol 9:1 (2 ml) which was 0.1 M in trifluoroacetic acid and stirred at room temperature. After 5 hours, the reaction was complete (as followed by tlc), the solution diluted with ether (10 ml) and washed with saturated sodium carbonate (2 x 10 ml) and aqueous saturated sodium chloride (1 x 10 ml). The organic solution was dried (Na_2SO_4) and the solvent removed to give 7 mg (40%) of 77 as a pale, yellow oil.

PHYSICAL DATA FOR 77

^{1}H nmr ($CDCl_3$): δ 1.15 (d, J_d=6.0, 3H), 1.8 (bs, 1H), 2.42 (m, 2H), 3.98 (m, 1H), 6.18 (m, 1H), 6.92 (m, 1H), 9.55 (d, J_d=8.0, 1H)

8-(2-Tetrahydropyranyl)oxy-3,5-nonadien-2-one (78)

A mixture of aldehyde 74 (50 mg, 0.25 mM) and phosphorane 88 (80 mg, 0.25 mM) was refluxed in dry benzene (2 ml) for 14 hours. The solvent was removed and the residue triturated with dry pentane (4 x 4 ml). The residue was chromatographed over silica gel (2.5 g) using pentane as eluent and gradually changing to pentane and ether 1:1, giving 45 mg (72%) of 77 as a pale, yellow liquid.

PHYSICAL DATA FOR 78

^{1}H nmr ($CDCl_3$): δ 1.12 (d, J_d=6.0, 3H), 1.4-2.0 (m, 6H), 2.1-2.7 (m, 2H), 2.24 (s, 3H), 3.45 (m, 1H), 3.82 (m, 2H), 4.61 (m, 1H), 6.22 (m, 3H), 7.05 (m, 1H)

8-Hydroxy-3,5-nonadiene-2-one (79)

The ketone 78 (24 mg, 0.1 mM) was dissolved in a solution of methanol 9:1 (1.4 ml) which was 0.1 M in trifluoroacetic acid. The mixture was stirred at room temperature for 16 hours after which time no starting material was apparent by tlc. Work up as for 77 gave a yellow oil. Column chromatography over silica gel (1 g) using chloroform as eluent and gradually changing to chloroform and methanol 19:1, gave 9 mg of a yellow oil.

PHYSICAL DATA FOR 79

^{1}H nmr ($CDCl_3$): δ 1.15 (d, J_d=6.0, 3H), 2.24 (s, 3H), 2.45 (m, 2H), 4.25 (m, 1H), 6.20 (m, 3H), 7.00 (m, 1H)

PART II: NEW REAGENTS FOR ORGANIC SYNTHESIS

CHAPTER 1: SELECTIVE AND DIRECT ACTIVATION OF O-ESTERS

CONVERSION OF PHENYL AND 2,2,2-TRIFLUOROETHYL ESTERS INTO ACYL IMIDAZOLIDES

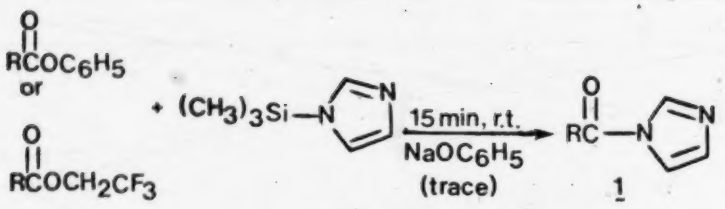
The protection and activation of carboxylic acids are important synthetic operations. Synthesis of naturally occurring macrolides often require: (1) differentiation between two (or more) carboxylic acids of a synthetic intermediate by means of appropriate protection, and (2) selective activation of only one group under mild, neutral conditions. A useful transformation in macrolide synthesis is one whereby only one of two O-esters (but not O- and S-mixed esters) of a compound could be converted selectively and directly into a reactive functional group that would be useful in subsequent operations. A problem commonly encountered during attempts at direct activation of esters is that the desired reaction is usually slow or proceeds more slowly than its reverse reaction (Equation 1).

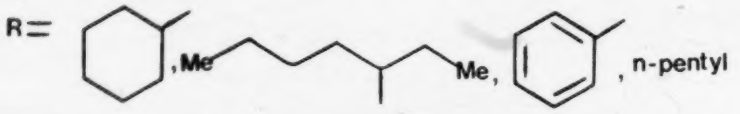
$$RCOOR' + Y^- \rightleftharpoons RCOY + {}^-OR' \qquad (1)$$

$$^-OR' + MY \longrightarrow MOR' + Y^- \qquad (2)$$

Suppression of the reverse reaction can be accomplished by removing $^{-}OR'$ in Equation 1, by selecting a proper reagent (MY in Equation 2). Requirements for MY are such that M^{+} is a hard acid with a strong affinity for oxygen and a soft base Y^{-} (relative to ^{-}OR). A good choice for M^{+} is $R_3''Si^{+}$. Phenyl and 2,2,2-trifluoroethyl (R') esters are both potential protective groups and can be readily converted into the corresponding acyl imidazolides upon treatment with N-trimethylsilylimidazole (MY) at room temperature. This reaction can be initiated by a trace amount of sodium phenoxide. In many ways, the acyl imidazolide (1) is similar in reactivity to that of an acid chloride.[119] Preparation of a triphenylacylmethylenephosphorane[136] and a ketoester using this species has been reported.[120]

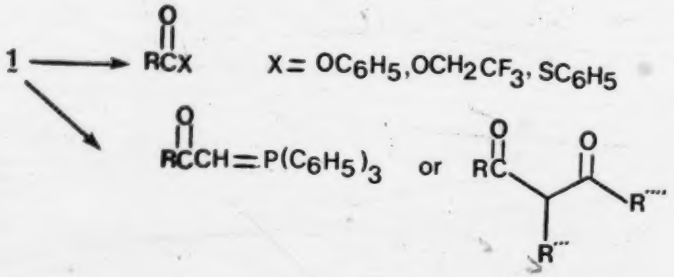
Formation of the acyl imidazolide proceeded well with phenyl esters of aromatic, primary and secondary carboxylic acids (in all cases, isolated yields were greater than 90%). Quantitative acyl imidazolide formation was also possible with the 2,2,2-trifluoroethyl esters of these carboxylic acids. Fortunately, S-tert-butylthiol and alkyl esters did not react nor did the benzenethiol esters. These esters were, therefore, distinguishable from phenyl and 2,2,2-trifluoroethyl esters.



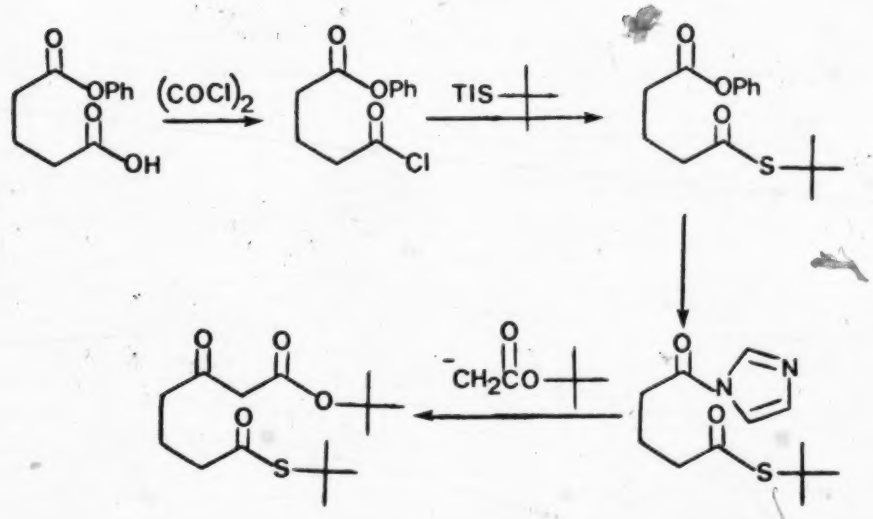


Esters of 2-methylphenol and 4-methoxyphenol are converted to the acyl imidazolides as rapidly as phenol, however, the 2,6-dimethyl phenol ester fails to react even in refluxing tetrahydrofuran, presumably because of steric demands.

Since acyl imidazolides behave similarly to acid chlorides, reaction with an ROH with sufficient acidity is expected to, and does, give the corresponding ester.



An example of the applicability of an acyl imidazolide which has been used as a model in macrolide synthesis is described.



The advantage offered by this procedure is that hydrolysis is not required in the activation of the ester, therefore eliminating the possibility of undesired side reactions such as reverse aldol condensations or dehydrations.

CHAPTER 2: EXPERIMENTAL

Preparation of Phenyl Esters

In a typical example, a solution of the corresponding acid chloride (0.034 M) in benzene (15 ml) was added dropwise to a cold (10°) stirred solution of the phenol (0.051 M) and pyridine (0.051 M) in benzene (60 ml). The reaction mixture was stirred at room temperature for 14 hours and then filtered through a sintered glass funnel. The organic solution was then washed successively with water (20 ml), aqueous 1 N hydrochloric acid (2 x 20 ml), water (20 ml), aqueous 5% sodium carbonate (2 x 20 ml), water (1 x 20 ml) and aqueous saturated sodium chloride (1 x 20 ml). The organic layer was dried (Na_2SO_4) and the solvent removed. Purification either by distillation or column chromatography gave the phenyl ester in almost quantitative yield. Substitution of the phenol for thiophenol gave the corresponding S-phenyl ester and substitution for trifluoroethanol gave the trifluoroethyl esters. The S-tert-butyl thiol ester was obtained as described in Part I of this thesis.[100]

Preparation of Imidazolides from Phenyl Esters

1 2

To a solution of phenyl cyclohexane carboxylate 1 (190 mg, 0.95 mM) in anhydrous tetrahydrofuran (10 ml) in an argon filled glove bag, were added sodium phenoxide (2.3 mg, 0.023 mM) and trimethylsilyl imidazolide (170 μl, 1.1 mM). The reaction mixture was stirred at room temperature for 15 minutes and the solvent removed under reduced pressure. The reaction could be followed by infrared spectroscopy since the starting ester appears at about 1760 cm^{-1} and the imidazolide at 1740 cm^{-1}. The side products that formed during the reaction were removed with a vacuum pump. To the remaining product was added cyclohexane (3 ml) and the solution was filtered. The solvent was removed under reduced pressure to give 159 mg (96%) of white solid 2. The reaction could also be carried out in cyclohexane as solvent, rather than tetrahydrofuran, with the same results.

PHYSICAL DATA FOR 2

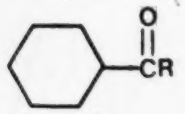
bp: 87-88° (0.3 mm)

ir (CCl_4): 1740 (s)

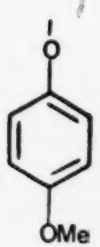
^1H nmr ($CDCl_3$): δ 1.3-2.0 (m, 10H), 2.9 (m, 1H), 7.17 (m, 1H), 7.53 (M, 1H), 8.25 (m, 1H)

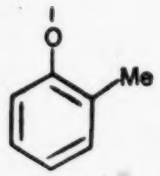
Mass Spectrum: calcd for $C_{10}H_{14}N_2O$: m/e = 178.1106
measured: m/e = 178.1104

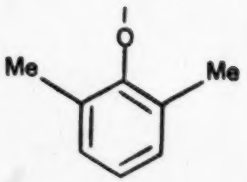
Table 8: Preparation of the Imidazolide from Other Esters[a]

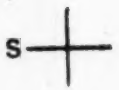


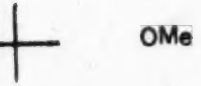
R









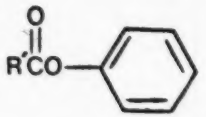


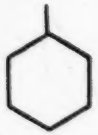
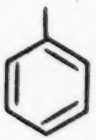
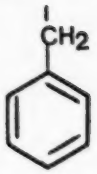
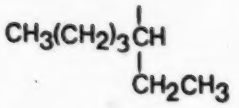
Percent Yield of Imidazolide	96	96	10[b]	10[b]	0	0
Compound	4	5	6	7	8	9

[a] The reaction time was 15 minutes in all cases

[b] Estimated by ir spectroscopy

Table 9: Imidazolides[a]



R					n-C_6H_{13}-
Percent Isolated Yield of Imidazolide	96	96[b]	86[b]	96[b]	86[b]
Ester, Imidazolide	1, 2	10, 14	11, 15	12, 16	13, 17

[a] The reaction time was 15 minutes in all cases

[b] Yield estimated by ^1H nmr

Preparation of Phenyl Esters from Imidazolides

2 1

To a stirred solution of imidazolide 2 (168 mg, 0.94 mM) in cyclohexane (10 ml) was added sodium phenoxide (2.3 mg, 0.023 mM) and phenol (104 mg, 1.1 mM). The reaction was stirred for 15 minutes during which time imidazole precipitated as a white solid. The reaction mixture was filtered and the solvent removed under reduced pressure to give 190 mg of residual oil which was purified by preparative thin layer chromatography, using chloroform as eluent, to give 184 mg of 1 as an oil.

PHYSICAL DATA FOR 1

bp: 94^{o} (0.5 mm)

ir (CCl_4): 1760 (s)

^1H nmr ($CDCl_3$): δ 1.0-2.3 (m, 11H), 7.0-7.6 (m, 5H)

Mass Spectrum: calcd for $C_{13}H_{16}O_2$: m/e = 204.1150
measured: m/e = 204.1151

Preparation of S-Phenyl Esters from Imidazolides

2 7

To a stirred solution of imidazolide 2 (168 mg, 0.94 mM) in cyclohexane (10 ml) was added sodium phenoxide (2.3 mg, 0.023 mM) and thiophenol (121 mg, 1.1 mM). The reaction was stirred for 15 minutes during which time imidazole precipitated as a white solid. The reaction mixture was filtered and the solvent removed to give 223 mg of oil which was purified by preparative thin layer chromatography, using Skelly B:ethyl acetate 19:1 as eluent, to give 213 mg (96%) of 7.

PHYSICAL DATA FOR 7

bp: 108° (0.11 mm)

ir (CCl_4): 1705 (s)

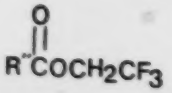
^1H nmr ($CDCl_3$): δ 1.05-2.5 (m, 11H), 7.38 (s, 5H)

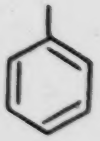
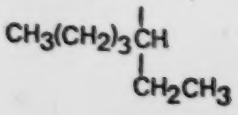
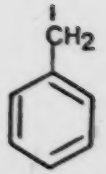
Preparation of Imidazolides from Trifluoroethyl Esters

3 2

To an argon purged flask containing a magnetic stirring bar was added sodium phenoxide (2.3 mg, 0.023 mM), after which it was fitted with a serum cap. The flask was placed inside an argon glove bag and trimethylsilyl imidazolide (170 μl, 1.1 mM), cyclohexane (10 ml) and trifluoroethyl ester 3 were added. The mixture was stirred for 45 minutes. The solvent was removed with a vacuum pump and the flask opened to an argon atmosphere. Carbon tetrachloride (4 ml) was added and removed with a vacuum pump to give 160 mg (95%) of white solid 2.

Table 10: Preparation of Imidazolide from Other Trifluoroethyl Esters[a]



			n-C_6H_{13}-	
Percent Isolated Yield of Imidazolide	94	96	97	0[b]
Ester, Imidazolide	18, 14	19, 16	20, 17	21, 15

[a] The reaction time was 45 minutes in all cases except the benzyl case, in which the reaction time was three hours

[b] This reaction did not work even after refluxing

Preparation of Trifluoroethyl Esters from Imidazolides

16 19

To a stirred solution of imidazolide 16 (193 mg, 1 mM) in cyclohexane was added sodium phenoxide (2.3 mg, 0.023 mM) and trifluoroethanol (101 mg, 1 mM). The reaction was stirred vigorously (since trifluoroethanol is only slightly soluble in cyclohexane) for 45 minutes during which time imidazole precipitated as a white solid. The reaction mixture was filtered and the solvent removed to give 218 mg (90%) of 19.

PHYSICAL DATA FOR 19

ir (CCl_4): 1760 (s)

^1H nmr ($CDCl_3$): δ 0.8-2.0 (m, 14H), 2.25 (q, 1H), 4.5 (q, 2H)

^{19}F nmr ($CDCl_3$): δ 6.97 (t)

Preparation of Trimethylsilyl Imidazole[121]

To hexamethyldisilazane (24.2 g, 150 mM) in a 50 ml flask was added imidazole (11 g, 162 mM) and two drops of concentrated sulphuric acid. The resulting mixture was refluxed at 100° for 30 minutes, and then at 140° for 2 hours. The reaction mixture was distilled (13 mm) making sure that the atmosphere contained only argon since the product was extremely moisture sensitive. Some low boiling material came over at 30° and the product distilled at 98-100°.

PHYSICAL DATA FOR TMSI

^{1}H nmr (CCl_4, external TMS): δ0.4 (s, 9H), 6.8 (s, 1H), 7.1 (s, 1H), 7.6 (s, 1H)

If moisture is present, proton exchange occurs and the ^{1}H nmr becomes δ0.4 (s, 9H), 7.1 (bs, 2H), 7.5 (bs, 1H).

PHYSICAL DATA FOR 3

^{1}H nmr ($CDCl_3$): δ 1.1-2.6 (m, 11H), 4.5 (q, 2H)

PHYSICAL DATA FOR 4

^{1}H nmr ($CDCl_3$): δ 1.1-2.2 (m, 11H), 3.8 (s, 3H), 6.95 (d, 4H)

PHYSICAL DATA FOR 5

^{1}H nmr ($CDCl_3$): δ 1.1-2.8 (m, 11H), 2.15 (s, 3H), 7.15 (m, 4H)

PHYSICAL DATA FOR 6

^{1}H nmr ($CDCl_3$): δ 1.1-2.8 (m, 11H), 2.1 (s, 6H), 7.05 (m, 3H)

PHYSICAL DATA FOR 8

^{1}H nmr ($CDCl_3$): δ 1.1-2.5 (m, 11H), 1.5 (s, 9H)

PHYSICAL DATA FOR 9

^{1}H nmr ($CDCl_3$): δ1.1-2.4 (m, 11H), 3.65 (s, 3H)

PHYSICAL DATA FOR 10

^{1}H nmr ($CDCl_3$): δ 7.4 (m, 4H), 8.5 (m, 4H)

PHYSICAL DATA FOR 11

^{1}H nmr ($CDCl_3$): δ3.9 (s, 2H), 7.4 (m, 10H)

PHYSICAL DATA FOR 12

^{1}H nmr ($CDCl_3$): δ0.8-2.2 (m, 14H), 2.5 (m, 1H), 7.25 (5H)

PHYSICAL DATA FOR 13

^{1}H nmr ($CDCl_3$): δ0.7-1.98 (m, 11H), 2.5 (t, 2H), 7.25 (m, 5H)

PHYSICAL DATA FOR 14

^{1}H nmr ($CDCl_3$): δ 7.1-8.2 (m, 8H)

PHYSICAL DATA FOR 15

^{1}H nmr ($CDCl_3$): δ4.2 (s, 2H), 7.1-7.7 (m, 7H), 8.2 (m, 1H)

PHYSICAL DATA FOR 16

^{1}H nmr ($CDCl_3$): δ0.7-2.1 (m, 14H), 2.95 (q, 1H), 7.15 (m, 1H), 7.65 (m, 1H), 8.3 (m, 1H)

PHYSICAL DATA FOR 17

^{1}H nmr ($CDCl_3$): δ0.8-2.7 (m, 11H), 2.9 (t, 2H), 7.15 (m, 1H), 7.60 (m, 1H), 8.3 (m, 1H)

PHYSICAL DATA FOR 18

^{1}H nmr ($CDCl_3$): δ4.7 (q, 2H), 7.3-8.2 (m, 5H)

PHYSICAL DATA FOR 20

^{1}H nmr ($CDCl_3$): δ0.8-2.0 (m, 11H), 2.4 (t, 2H); 4.5 (q, 2H)

PHYSICAL DATA FOR 21

^{1}H nmr ($CDCl_3$): δ3.5 (s, 2H), 4.35 (q, 2H), 7.2 (m, 5H)

Preparation of Glutaric Anhydride (22)

22

The procedure followed was that reported by H.D. Zook and J.A. Knight.[122] The reaction was carried out in the fume hood due to the evolution of HCl.

A mixture of glutaric acid (13.2 g, 100 mM) and freshly distilled acetyl chloride (23.6 g, 300 mM) was refluxed for 3 hours. The reaction was cooled to room temperature and the excess acetyl chloride and acetic anhydride formed in the reaction removed under reduced pressure using a water aspirator. The oily residue crystallized upon scratching and the crude product was recrystallized from ether to give 10.4 g (91%) of white solid.

PHYSICAL DATA FOR 22

mp: 54-56°

ir ($CHCl_3$): 1815 (s), 1770 (s)

^1H nmr ($CDCl_3$): δ 2.1 (m, 2H), 2.8 (m, 4H)

Preparation of Phenyl Hydrogen Glutarate (23)

22 23

The procedure followed was that reported by H. Vogt and W. Rosenberg.[123]

A mixture of glutaric anhydride (10.0 g, 87.6 mM) and phenol (8.25 g, 87.6 mM) was heated to 130° for 2 hours. The oily product was distilled at reduced pressure to give 14.2 g of product (bp 158-163°, 0.5 mm). This material was dissolved in ether (300 ml) and extracted with aqueous saturated sodium bicarbonate (5 x 50 ml). The aqueous layer was cooled to 5° and cautiously acidified with aqueous 2 N hydrochloric acid and then extracted with toluene (5 x 100 ml). The combined extract was dried (Na_2SO_4) and evaporated to give 9.6 g (53%) of white crystals.

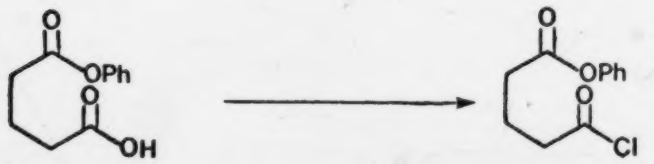
PHYSICAL DATA FOR 23

mp: 43-44°

ir ($CHCl_3$): 3500-2500 (bs), 1760 (s), 1710 (s)

^{1}H nmr ($CDCl_3$): δ 2.1 (m, 2H), 2.5 (m, 4H), 7.3 (m, 5H)
10.5 (s, 1H)

Preparation of Phenyl Chloro Glutarate (24)



23 → 24

To a stirred solution of 23 (1.04 g, 5.0 mM) in anhydrous benzene (40 ml) was added oxalyl chloride (1.9 g, 15 mM). The reaction was stirred at room temperature for 3 hours and the solvent and excess oxalyl chloride removed under reduced pressure to give 1.13 g (100%) of a colorless liquid which was used directly in the next step.

PHYSICAL DATA FOR 24

ir ($CHCl_3$): 1800 (s), 1760 (s)

^1H nmr ($CDCl_3$): δ2.15 (m, 2H), 2.65 (m, 2H), 3.05 (m, 2H), 7.3 (m, 5H)

Preparation of Phenyl S-tert-Butyl Glutarate (25)

24 25

To an ice-cooled solution of 24 (1.13 g, 5.0 mM) in anhydrous ether (40 ml) was added thallium (I) 2-methylpropane-2-thiolate (1.45 g, 5.0 mM). The yellow color of the thiolate discharged immediately. The reaction was stirred for ca. 2 hours at room temperature in order to allow the thallium (I) chloride produced in the reaction to coagulate. The reaction was filtered through Celite and the ether washed with aqueous 0.5 N hydrochloric acid, aqueous saturated sodium bicarbonate and aqueous saturated sodium chloride. The ether was dried (Na_2SO_4) and evaporated. The product was distilled to give 1.36 g (97%) of a colorless liquid.

PHYSICAL DATA FOR 25

bp: 120^{o} (0.05 mm)

ir ($CHCl_3$): 1760 (s), 1680 (s)

^{1}H nmr ($CDCl_3$): δ 1.5 (s, 9H), 2.2 (m, 2H), 2.65 (m, 4H), 7.3 (m, 5H)

Elemental Analysis:

calcd for $C_{15}H_{20}O_3S$:	C 64.26,	H 7.19
	O 17.12,	S 11.44
found:	C 64.20,	H 7.16
	O 17.17,	S 11.46

Preparation of Imidazole S-tert-Butyl Glutarate (26)

25 26

To a solution of 25 (280 mg, 1.0 mM) in anhydrous tetrahydrofuran (10 ml) was added trimethylsilyl imidazole (150 μl, 1.1 mM) and sodium phenoxide (10 mg, 0.1 mM). The solution was stirred at room temperature for 1 hour and the solvent evaporated. The residue was left on high vacuum (0.01 mm) for 1 hour in order to remove volatile side products and unreacted trimethylsilyl imidazole. The residue was dissolved in cyclohexane (10 ml) and filtered to remove the catalyst. The solvent was evaporated to give 260 mg (100%), due to a small amount of trimethylsilyl phenol still present, of a colorless liquid which was used directly for the next reaction.

PHYSICAL DATA FOR 26

ir ($CHCl_3$): 1741 (s), 1680 (s)

^1H nmr ($CDCl_3$): δ1.45 (s, 9H), 2.1 (m, 2H), 2.55 (m, 2H),

2.9 (m, 2H), 7.05 (m, 1H), 7.45 (m, 1H),
8.15 (m, 1H)

Preparation of tert-Butyl Trimethylsilyl Acetate (27)

27

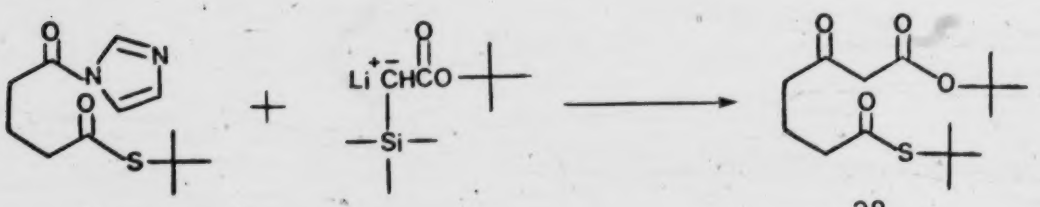
The procedure followed was that reported by M.W. Rathke.[124]

To anhydrous tetrahydrofuran (150 ml) was added n-butyllithium in hexane (38 ml, 1.3 M, 50 mM). The solution was cooled to 0° and diisopropylamine (5.15 g, 51 mM) was added dropwise over 5 minutes. After 10 minutes at 0°, the solution was cooled to -78° and tert-butyl acetate (5.8 g, 50 mM) was added dropwise over 10 minutes. The reaction was stirred at -78° for 30 minutes and freshly distilled trimethylchlorosilane was added (20 ml, large excess) and then the cooling bath was removed. After the reaction reached room temperature, the solvent was evaporated at 0° under reduced pressure. The residual liquid (containing LiCl) was distilled under reduced pressure to give 8.6 g (91%) of a colorless liquid.

PHYSICAL DATA FOR 27

bp:	67° (13 mm)
ir (neat)	1715 (s)
^{1}H nmr ($CDCl_3$):	δ0.05 (s, 9H), 1.35 (s, 9H), 1.80 (s, 2H)

Acylation of Imidazole S-tert-Butyl Glutarate (28)



26 + Li⁺⁻CHCO(Si) → 28

The procedure followed was that reported by M.W. Rathke.[124]

To anhydrous tetrahydrofuran (10 ml) was added n-butyllithium in hexane (770 μl, 1.3 M, 1.0 mM). The solution was cooled to 0° and diisopropylamine (110 mg, 1.1 mM) was added. After 1 minute, the solution was cooled to -78° and tert-butyl trimethylsilylacetate 27 (188 mg, 1.0 mM) in anhydrous tetrahydrofuran (1 ml) was added dropwise over 5 minutes. The cloudy solution was stirred at -78° for 10 minutes and imidazole 26 (254 mg, 1.0 mM) in anhydrous tetrahydrofuran (1 ml) was added dropwise over 5 minutes to produce a clear yellow solution. The reaction was stirred at -78° for 1 hour and the cooling bath removed. After 15 minutes, the reaction was quenched with aqueous 2 N hydrochloric acid. The reaction was concentrated to ca. 2 ml and diluted with toluene (25 ml). The organic layer was washed with aqueous 0.5 N hydrochloric acid, aqueous sat-

urated sodium bicarbonate, aqueous saturated sodium chloride, dried (Na_2SO_4) and the solvent evaporated. The residue was chromatographed over silicic acid (15 g) using ether:hexane 1:1 as eluent to give 208 mg (69%) of 28 as a colorless liquid.

PHYSICAL DATA FOR 28

ir ($CHCl_3$): 1740 (s), 1712 (s), 1680 (s)

^1H nmr ($CDCl_3$): δ1.50 (s, 18H), 2.0 (m, 2H), 2.5 (m, 4H), 3.3 (s, 2H)

Elemental Analysis: calcd for $C_{15}H_{26}O_4S$: C 59.57, H 8.67, O 21.16, S 10.60

found: C 59.46, H 8.63 O 20.32, S 10.32

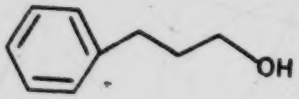
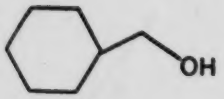
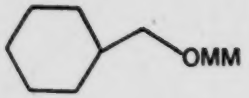
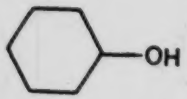
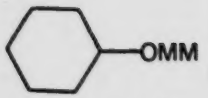
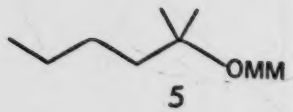
CHAPTER 3: PROTECTION OF HYDROXYL AND CARBOXYL GROUPS

In connection with the synthesis of macrolide antibiotics, there arises a need for a new protecting group that serves to protect both hydroxyl and carboxyl functions. This group should be reasonably stable towards acid and base, and should satisfy the usual criteria of a protecting group - efficient blocking and deblocking. The MEM blocking group[125] and selectivity of trimethylsilyl iodide[126] in hydrolysis of benzyl and tert-butyl esters, suggested the methoxy methyl group which has not been widely used due to the drastic conditions necessary for its removal. We have found the use of trimethylsilyl bromide is a partial solution to this problem.

The formation of MM ethers of primary, secondary and tertiary alcohols, and primary and secondary esters, proceeds cleanly and in reasonably good yield. Some examples are included in Tables 11 and 12.

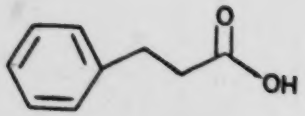
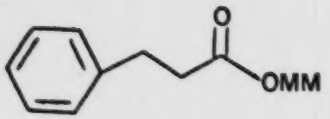
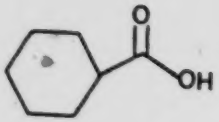
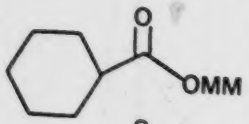
A comparative study of the acid stability of several acetals as 0.1 M solutions in anhydrous methanol containing 0.2 equivalents of trifluoroacetic acid, at room temperature, gave the following times for complete hydrolysis as followed by glpc: 9 (<10 minutes), 10 (3 hours) and 11 (5 hours). The MM ether was recovered quantitatively even after one week under these conditions.

Table 11: Preparation of MM Ethers ROMM[a] (1)

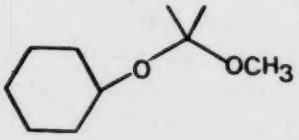
Alcohol	Reaction Time (Hours)	Product	Percent Yield
	3	**2**	95
	3	 **3**	95
	3	 **4**	95
	3	 **5**	85

[a] MM = CH_2OCH_3

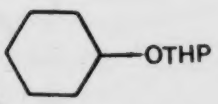
Table 12: Preparation of MM Esters RCO_2MM[a] (6)

Acid	Reaction Time (Hours)	Product	Percent Yield
	3	 7	95
	3	 8	95

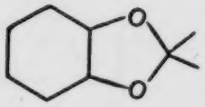
[a] MM = CH_2OCH_3



9



10



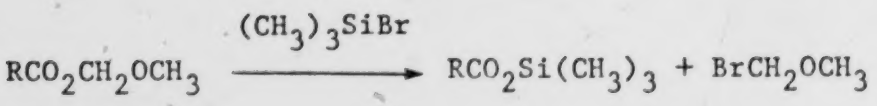
11

Compounds 3, 4 and 5 were recovered in nearly quantitative yield when a 0.5 M solution was treated with (1) 6:1 acetic acid, H_2O, 5 hours; (2) trifluoroacetic acid, 2 equivalents, methanol or tetrahydrofuran, 16 hours; (3) aqueous 2 N sulphuric acid, 2 equivalents, tetrahydrofuran, 16 hours; (4) zinc, 5 equivalents, acetic acid, and (5) pyridinium chlorochromate, 1.5 equivalents, dichloromethane, 2 hours. The same compounds were stable to Lewis acids zinc bromide and magnesium bromide (5 equivalents, dichloromethane, 16 hours), but readily cleaved by strong Lewis acids such as aluminum trichloride and titanium tetrachloride. Compounds 3, 4 and 5 were recovered quantitatively after treatment under conditions for ester hydrolysis (aqueous sodium hydroxide, tert-butyl alcohol, 16 hours) and thiolester hydrolysis (mercuric trifluoroacetate, acetonitrile, 2 hours). Bromotrimethylsilane[127] was found to cleave methoxy methyl ethers (Equation 1). By quenching the mixture with anhydrous methanol, the corresponding alcohol was obtained in ca. 90% yield.

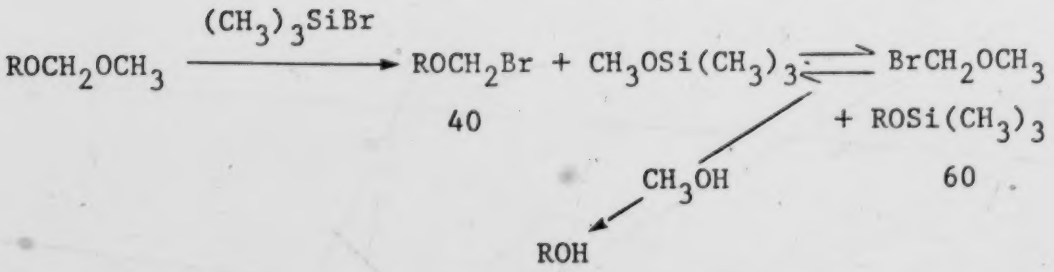
$$ROCH_2OCH_3 \xrightarrow{(CH_3)_3SiBr} ROCH_2Br + ROSi(CH_3)_3 + CH_3OSi(CH_3)_3 + BrCH_2OCH_3$$

Equation 1

The methoxy methyl protected acids also showed similar stability. The esters 7 and 8 were recovered in nearly quantitative yield from the following conditions as a 0.5 M solution in (1) 6:1 acetic acid, H_2O, 5 hours, 20°, (2) trifluoroacetic acid, 2 equivalents in methanol or tetrahydrofuran, 16 hours, 20°, (3) aqueous 2 N sulphuric acid in tetrahydrofuran, 16 hours, 20°, (4) zinc, 5 equivalents, in acetic acid, 5 hours, 20°, and (5) pyridinium chlorochromate, 1.5 equivalents, in dichloromethane, 1.5 hours. The ester was cleaved by mild acids such as zinc bromide, 5 equivalents, in dichlormethane, 16 hours, 20° and was hydrolyzed under alkaline conditions at a rate comparable to a methyl ester. The methoxy methyl group was also cleaved readily with bromotrimethylsilane. The possibility of distinguishing between the methoxy methyl ester and methoxy methyl ether was investigated. Adding one equivalent of trimethylsilylbromide to a 50:50 solution of MM ester:MM ether did not show any selectivity as followed by ^{1}H-NMR. Cleavage of both MM ester and MM ether was followed by ^{1}H-NMR using 4 and 8 (Equations 2 and 3).



Equation 2



Equation 3

This may be an SN2 type displacement and the stable carboxylate anion is a good leaving group. The ether gives an equilibrium which, upon quenching with dry methanol, gives the alcohol possibly by a series of equilibria, depending on the size of R. The reaction is possibly acid catalyzed and all attempts to successfully quench the reaction under neutral conditions failed. Quenching with (1) sodium bicarbonate in methanol, (2) sodium phosphate, dibasic in methanol, (3) triethylamine in methanol, and (4) sodium acetate in methanol, gave a mixture of starting material, diether 12 and a small amount of alcohol.

$ROCH_2OR$

12

It was also found that a thiol ester, subject to the trimethylsilylbromide methanol reaction, was converted to its methyl ester.

CHAPTER 4: EXPERIMENTAL

Preparation of Hexamethyldisiloxane (13)

$$(CH_3)_3SiCl + H_2O + C_6H_5N(CH_3)_2 \xrightarrow{\Delta} ((CH_3)_3Si)_2O$$

13

A solution of freshly distilled dimethylanaline (72.7 g, 76 ml, 0.060 M) and water (7.0 g, 0.389 M) was placed in a 250 ml 3-necked, round bottom flask equipped with a dropping funnel, reflux condenser, magnetic stirring bar and nitrogen inlet. Chlorotrimethylsilane (62.49 g, 73 ml, 0.575 M) was added dropwise over 50 minutes with stirring. The reaction mixture was refluxed for 1 hour (bath temperature, 125°). The reflux condenser was replaced by a distillation head and the product distilled at atmospheric pressure, followed by drying ($MgSO_4$), with stirring for 30 minutes, to give 39 g (76%) of hexamethyldisiloxane as a clear, colorless liquid.

PHYSICAL DATA FOR 13

bp: 101° (690 mm)

^{1}H nmr ($CDCl_3$): δ (External TMS) -0.1 (s)

Preparation of Trimethylsilylbromide (14)

$$((CH_3)_3Si)_2O \xrightarrow{PBr_3} (CH_3)_3SiBr$$

13 14

The procedure followed was that reported by W.F. Gilliam, R.N. Meals and Robert O. Sauer.[127]

Into a pressure bottle was weighed hexamethyldisiloxane 13 (32.6 g, 0.2 M), phosphorous tribromide (156 g, 0.34 M) and iron III chloride hexahydrate (0.4 g) and the contents mixed thoroughly by shaking. After standing 24 hours at room temperature, the reaction was distilled through a large Vigreux column and the fraction boiling at 80° collected. The reactive trimethylsilylbromide was used as a 0.3 M solution in dry carbon tetrachloride.

PHYSICAL DATA FOR 14

^1H nmr (CCl_4): δ(External TMS) 0.56 (s)

Preparation of MM Ethers and MM Esters

To the alcohol or acid (1.0 mM), in dry dichloromethane (5 ml) at 0°C, was added diisopropylethylamine (1.05 mM) followed by chloromethyl methyl ether (1.05 mM). Such a hindered base is necessary for this reaction. The reaction was allowed to warm to room temperature and stirred for 3 hours. Upon completion of the reaction, the dichloromethane layer was washed with aqueous 0.1 N sulphuric acid, aqueous saturated sodium chloride and dried (Na_2SO_4). After evaporation of solvent and purification, the MM ether and MM ester were confirmed by ir and ^1H nmr spectroscopy.

Cleavage of the MM Protecting Group

To the MM protected ether or ester (1 mM) in dry carbon tetrachloride was added trimethylsilylbromide (1.1 mM). The final concentration of the solution was ca. 0.15 in reactant and reagent. The mixture was vigorously stirred for 5 minutes and diluted with a tenfold excess of methanol. Evaporation of solvents gave an oily residue which was dissolved in benzene, washed with water, aqueous saturated sodium chloride and dried (Na_2SO_4). Evaporation of solvent gave the product in 90 to 95% yield.

PHYSICAL DATA FOR 2

bp: 110-112° (8.0 mm)

^{1}H nmr ($CDCl_3$): δ1.82 (m, 2H), 2.72 (m, 2H), 3.40 (s, 3H), 3.72 (t, 2H), 4.62 (s, 2H), 7.22 (s, 5H)

PHYSICAL DATA FOR 3

bp: 110° (40 mm)

^{1}H nmr ($CDCl_3$): δ0.85-1.98 (bm, 11H), 3.33 (m, 2H), 3.38 (s, 3H), 4.52 (s, 2H)

PHYSICAL DATA FOR 4

bp: 115° (50 mm)

^{1}H nmr ($CDCl_3$): δ0.80-1.92 (bm, 11H), 3.35 (s, 3H), 4.55 (s, 2H)

PHYSICAL DATA FOR 5

bp: 120° (15 mm)

^{1}H nmr ($CDCl_3$): δ0.92-1.48 (m, 15H), 3.34 (s, 3H), 4.60 (s, 2H)

PHYSICAL DATA FOR 7

bp: 108° (5 mm)

^{1}H nmr ($CDCl_3$): δ 0.85-2.25 (bm, 11H), 3.45 (s, 3H), 5.21 (s, 2H)

PHYSICAL DATA FOR 8

bp: 110° (3 mm)

^{1}H nmr ($CDCl_3$): δ 2.50-3.22 (m, 4H), 3.42 (s, 3H), 5.22 (s, 2H), 7.26 (s, 5H)

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